PEDIATRIC CLINICS OF NORTH AMERICA

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FOREWORD

WILLIAM A. REILLY, M.D.
Consulting Editor

Topics for this Symposium were selected for newer practical and useful information for practitioners, investigators and students. Each of the writers has stressed therapy, as well as diagnosis.

The Editor is impressed with the developments in enzymology and genetics. Recent developments in endocrinology reveal that there are many abnormalities of enzymes, genetically conditioned, which are the causes for some of the heretofore little understood clinical syndromes. Childs' and Sudbury's review of modern genetics, as it applied to problems of medicine,* contains helpful information on endocrine and other conditions genetically determined.

Some examples of enzyme defects in this Symposium are dwarfism with galactosemia and glycogen storage disease (absence of glucose-6-phosphatase). Examples of genetic conditioning are obesity and genetic dwarfism (in rats), goitrous hypothyroidism (the failure to organify iodine production of mature thyroid hormone), intersex and congenital adrenal cortical hyperplasia.

* *Pediatrics*, 20:178, 1957.

DIABETES MELLITUS IN CHILDREN

FRANCIS SCOTT SMYTH, M.D.

DEFINITION AND HISTORY

Diabetes mellitus is a derangement of metabolism involving the utilization of carbohydrate and manifested by glycosuria, ketone acidosis, and hyperglycemia.

The disease was recognized symptomatically in the first century, but the identification of sugar in the urine awaited the experiments of Dobson in 1755. While Claude Bernard attributed the excess production of sugar to the liver, the important role of the pancreas became evident from the extirpation experiments of von Mering and Minkowski.[10] The essential internal secretion of the pancreas—insulin—was extracted and identified by Banting and Best in 1922.[1] Epinephrine was found to counteract some of the effects of insulin, and, more recently, the experimental investigations of Houssay,[6] Young,[15] and Long[9] and others have elucidated the role of other endocrine glands in the production of diabetogenic agents or insulin antagonists. Thus the experimental laboratory has elucidated not only the production of diabetes, but also the probable mechanism of deranged sugar metabolism in diseases of the pituitary and adrenal glands.

Important, however, as the contributions from the experimental field have been, the majority of patients with clinical diabetes do not present the exact counterpart. There is still no clear-cut understanding of the etiology of clinical diabetes, though several factors are recognized, such as heredity, infection and "endocrine imbalance."

Familial incidence is of such importance that no history can be complete without a careful search for the incidence of the diabetic trait, which has been suggested as being carried by a recessive genetic factor.

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Infection frequently precipitates, and certainly aggravates, diabetes mellitus. In diabetes associated with mumps infection there would seem to be a direct insult to the insulin-producing islet tissue, but the majority of infections without a predilection for glandular tissue act antagonistically to insulin.

The interrelation of other hormones with insulin is even more difficult to interpret. Diabetes can be produced experimentally by extirpation of the pancreas and/or injection of pituitary extracts. The adrenal, likewise, has been shown to produce insulin antagonists, and the alpha cells of the islets have been found to produce (?glucagon) an insulin inhibitor. In hyperthyroid states with disturbed sugar metabolism, thyroidectomy was at one time proposed for alleviation of diabetes mellitus; even the gonads may be involved. As a result of these varied observations, many disturbances in carbohydrate metabolism in diseases which involve endocrine glands can be explained (Paget's disease, Addison's disease and Graves' disease), but function and pathology cannot yet be correlated in most patients with diabetes mellitus.

The pathology of the pancreas in clinical diabetes is usually disappointing, although radioactive isotope deposition in tissues can throw some light on this. Hydropic degeneration, islet counts, and so forth, do not parallel the production or efficiency of insulin. Although pancreatitis and some cases of pancreatic fibrosis may have a related diabetic state, most autopsies do not show such lesions in the pancreas or such gross changes in the other endocrine glands. The liver, which is vital as the chief site of glycogen reserve, sometimes shows secondary fatty infiltration, or in diabetes which is treated inadequately. Usually the recognized lesion is vascular and relates to the secondary degenerative changes in long-standing diabetes (Kimmelsteil-Wilson syndrome).

Childhood vs. Adult Diabetes

The diabetes of children differs in some respects from that of adults. About one third of the diabetes in children occurs during a period of rapid growth. The classical triad of symptoms—polyphagia, polyuria and polydypsia—is more characteristic of older diabetics. Children under five years of age often manifest polyuria and polydypsia, but lack polyphagia to a degree of anorexia. Obesity or overweight, which is a frequent concomitant in adult diabetes, plays no part in the picture of the diabetes in childhood. Arterial disease in older diabetics occurs with sufficient frequency to suggest that transport and utilization, rather than suppression of insulin, accounts for the diabetes which often requires no insulin.

Juvenile diabetes is usually a serious condition which develops rapidly and necessitates heroic intervention. Children, in comparison with adults, have poor reserves of glycogen, as well as fluid and electrolytes;

acidosis and dehydration are more frequent and severe. On the other hand, the young person has a resilience and a reparative capacity which is manifested by the shorter recovery periods from coma. Generally, the juvenile diabetic responds more quickly and dramatically to insulin. He is insulin-sensitive, in contrast with many adults who require larger amounts of insulin and are relatively insensitive to it.

DIAGNOSIS

With manifestations of increased thirst and urination, the indication for urinalysis is obvious. In the very young, diapered infant, however, frequency of urination is not apt to be noted. These infants on formula or breast feeding may have increased thirst which is rarely detected, and are more likely to come to medical attention because of vomiting associated with the hyperpnea of acidosis and dehydration. In older infants and children, polyuria and polydypsia are likely to attract attention. It may be found that a previously trained child becomes an enuretic or urinates several times during the night, or fails to gain weight or suffers loss of weight. Also, increased appetite in these young infants is not so apparent as in older children (six to 12) and adults.

Inasmuch as the major defect in diabetes mellitus is concerned with the metabolism of carbohydrate, glycosuria is perhaps the earliest and most common manifestation. Alertness and the increased use of the simplified tests for glycosuria are responsible for the discovery of more cases and at earlier stages of diabetes than formerly.[8] Although detection campaigns are based largely upon the routine testing of urine for the presence of glucose, the presence of a reducing agent is not diagnostic per se. It may be necessary to prove the nature of the reducing agent unless, as is true for some of the enzyme tests, the test is specific for glucose.

Except in the earliest stages of diabetes, ketonuria is usually present, and one should hesitate to base a diagnosis on glycosuria without ketonuria. Glycosuria, as an initial clue to the presence of diabetes mellitus, becomes important if it reflects an elevated blood sugar level, though it is occasionally found without significant elevation of the blood sugar. In such cases of "renal glycosuria" the kidney fails to reabsorb the glucose, even though the blood sugar is not elevated to the range of the so-called renal threshold (175 or more mg. per 100 ml.). The most frequent cause of glycosuria in children is alimentary glycosuria—a transient phenomenon due to the sudden ingestion of a large amount of concentrated carbohydrate (candy). Ketonuria is absent in such instances.

Hyperglycemia may be apparent at once from a specimen of blood under fasting conditions, or it may be appraised more accurately by the

glucose tolerance test. The test is useful in the very mild or prediabetic state, but is not indicated in the majority of diabetic children who come to the physician's attention with glycosuria, acetonuria, hyperglycemia and evidence of dehydration and acidosis.

TREATMENT—ACUTE STAGE

The occasional juvenile diabetic who is not toxic or febrile with an infection, and whose mild acidosis is not complicated by vomiting, will respond to oral fluids and insulin injection. More frequently, however, the acidosis is severe and vomiting prevents the use of the oral route of administration. In some cases the dehydration is of such a degree that it would not respond to the limited oral capacity even if vomiting were not present. For these the proper use of fluid and electrolytes, and insulin, are spectacular and, at times, lifesaving.

Fluid and Electrolyte

In severe dehydration and acidosis the body loses base in the excretion of excess acid. Considerable improvement can be obtained by a slow drip of normal saline or Ringer's solution, which can be given subcutaneously together with simultaneous administration of glucose intravenously (this, as described above, with insulin). However, no base (sodium) is available in these solutions to meet the deficit, although in sixth-molar lactate solution, sodium combined with the organic lactate radical meets this need. Barring extreme liver damage, the lactate is slightly antiketogenic, slowly metabolized, and leaves the sodium available for the body's needs. Hence the sixth-molar Ringer lactate solution is ideal both for acidosis and dehydration, can be given intravenously or subcutaneously, and without hazard if the patient is voiding. No exact dosage is necessary, although it is usual to use about 20 cc. per kilogram for intravenous administration and 40 cc. per kilogram for subcutaneous administration.

Occasionally, in comatose patients with deep hyperpnea, when the acidosis may be of such a dangerous degree that replacement of sodium from the Ringer lactate solution is too slow, there is need for intravenous administration of sodium bicarbonate itself. Bicarbonate is available for addition to intravenous fluids; it can be used directly from the commercial packages in 5 per cent strength, or added to glucose or saline solution. When given alone, a 6 per cent solution is made with triple-distilled water previously boiled or autoclaved. The bicarbonate itself must not be heated, but added when the solution is just above body temperature. The amount of bicarbonate can be gauged in the same manner by which the initial insulin dosage is calculated:

Normal concentration of $NaHCO_3$ in body fluids equals 0.3 per cent (60 vol. % CO_2 or 27 mEq. HCO_3).
Body fluids approximate two thirds of body weight in kilograms.
A reduction of one fourth the normal content of $NaHCO_3$ (15 vols. % CO_2 or 6.5 mEq. HCO_3) would mean a deficit of one fourth (two thirds of body weight in kilograms) times 3 gm. $NaHCO_3$, or 0.5 gm. per kilogram.

Since 0.5 gm. per kilogram will supply one fourth of the normal body content, this dosage is safe to use even if the exact base deficit is not known. In extreme acidosis the immediate restoration of one fourth the body content of sodium bicarbonate is a safe emergency procedure. Potassium is not advocated until adequate diuresis has been obtained. When used, it can be given in an 8 per cent solution (mEq.) in orange juice and beef broth.

In the acute diabetic stage parenteral fluid therapy may have to be continued over many hours. Laboratory determinations for glucose and electrolyte levels in the blood are most helpful. In their absence, urine findings and the clinical appearance of the patient can act as a guide for subsequent therapy. It is desirable to check for dry, impacted feces which are attributable to the extreme dehydration and which may seriously interfere with, or delay, the resumption of oral alimentation. A cleansing enema, followed by an oil retention enema, may prove beneficial.

When oral feedings are started, fruit juices or artificial "lemonade" (sodium lactate-lactic acid mixture) can be used. Orange juice, given at frequent intervals, but in moderate amounts, is usually well tolerated.

Insulin

During the acute stage of onset, the juvenile is almost totally diabetic; with improvement, endogenous insulin production usually becomes apparent. During this recovery period it is better to continue the use of standard insulin, the effects of which last no longer than four or five hours. Hypoglycemia, which often characterizes this period, can be promptly corrected and the standard insulin dosage more quickly adjusted.

When hypoglycemia occurs, it is desirable to get a simultaneous blood sugar determination and to note the patient's symptoms, which may vary in the same individual, but especially from those of other diabetics. Some children may have markedly altered disposition; others may resort to violent aggressive behavior, become sleepy, lapse into coma, develop strabismus or have convulsions. Symptoms may develop at blood sugar levels which are not low, but which represent a rapid fall from high levels, and usually begin when the blood sugar is around 70 mg. per 100 ml. Some patients, however, are free from symptoms and are alert

even when the blood sugar is as low as 20 mg. Relief is quickly obtained when sugar or fruit juice is administered. With convulsions, the hypoglycemia may require intravenous administration of glucose, 5 or 10 mg. per 100 ml. By giving this slowly and measuring the amount, one can avoid unnecessary excess and make a rough calculation of the equivalent standard insulin excess to be met.

In some clinics, such as the University of Iowa, diabetic children are maintained on standard insulin only. There is considerable justification for this, since the blood sugar can be kept in the normal range throughout the 24-hour period and more rapid adjustments of the insulin dosage can be made when indicated. Nevertheless, repeated injections of insulin, especially the night administration, are difficult for the usual family to manage, while midday injections complicate the routine of the child in school. The addition of proteins, such as protamine and globin, delays the absorption of injected insulin and prolongs its action. Regular or crystalline zinc insulin has an effect on the blood sugar in about 20 minutes, a maximum activity in about three hours, and no effect after seven hours. Protamine zinc insulin has an effect in 10 hours, is maximal at 18 hours, and ineffective after 24 hours.

For the more severe diabetic state, therefore, a combination of slowly absorbed insulin with standard insulin has been found to be satisfactory. Despite theoretical objections, we have used PZI (protamine zinc insulin) and standard insulin simultaneously, in the same syringe. The PZI is first drawn into the syringe followed by standard insulin; though some mixing does occur, the immediate effect of the standard insulin is still manifest. The proportions used are in the range of 3:1; i.e., a child who receives 20 units of standard insulin before breakfast (and 10 units each at noon and night) may be tried on an injection of 20 units of standard insulin and 10 units of PZI. Subsequent adjustments can be made on the basis of the time-occurrence, amount of glycosuria, and microsugars during the 24-hour period.

More recently it has been found that the prolongation of insulin action may be influenced by the size of the insulin crystals. The larger crystalline insulin known as lente insulin acts as long as does PZI. Semi-lente insulin from smaller crystals is intermediate, while lente insulin (a mixture of 70 per cent ultralente and thirty per cent semilente) has an action time similar to NPH (neutral protamine Hagedonn) of 12 to 15 hours. These newer preparations avoid the use of added protein and may make it possible to individualize the insulin dosage more accurately.

Evidence suggests that exogenous insulin is subject to a binding action by the proteins of the blood—largely the gamma globulin. This may represent an antigen-antibody response, but its effect is to reduce the efficiency of the administered insulin. Such an action probably

accounts for the increase in insulin requirement after two to three months of insulin therapy and perhaps contributes to the "insulin resistance" in those patients, particularly older diabetics, who require very large doses of insulin.

During growth spurts, such as during adolescence, the diabetic may require an increase of insulin which may not be entirely compatible with his increase in size. Whether this is a diabetogenic effect of the somatotropic or growth hormone is not clear.

Besides the binding action of serum proteins with insulin, other tissue factors have been found which may account for its inactivation or destruction.[11] These substances—notably in the liver—have been extracted in crude form and require adjusted pH and incubation, and suggest an enzyme system to which the term "insulinase" has been applied. The counterpart, or opposing tissue factor which reduces the action of "insulinase," has been called insulinase-inhibitor. The insulinase factor of the liver of the experimental animal (rat) is lessened by fasting the animal. Per unit of liver tissue, the insulinase is uninfluenced by the type of diet fed to the animal, although on a high carbohydrate diet the total weight of the liver is greater in proportion to the body weight of the animal; therefore such animals contained more insulinase per unit of body weight. These factors suggest that insulin efficiency may depend on the relative activity of insulin destruction by insulinase or of its preservation by the insulinase-inhibitor.

Investigations continue to elucidate the role of hormones and metabolic regulators which, in time, may offer practical aid in the control of diabetes. Foglia and co-workers[3] have shown an ameliorating effect of estrogens on the onset of diabetes in the pancreatectomized rat. A similar "protective" action of adrenal corticoids in initial stages of experimental diabetes has been reported by Houssay et al.[7] White[14] found no clinical effect of cortisone on the natural course of the disease, although estrogen was responsible for a 50 per cent drop in insulin requirement during a pilot study in diabetic pregnancy.

A number of years ago an extract of myrtle (Myrtillin) was given some trial as a hypoglycemic agent, until it was found to achieve its effect by injury to the liver. More recently, interest has been directed to agents which might fortify the insulin by reducing the action of inhibitors and insulin antagonists or by combating factors which bind or rapidly destroy insulin. Two such agents are now being studied. These are sulfonamides and are given by mouth: carbutamide and tolbutamide (Orinase).

Carbutamide lowers the blood sugar in some, but not all, diabetics. Since no effect can be obtained in pancreatectomized animals, the effect is apparently due to an increase in the efficiency of endogenous insulin. There seems to be little or no effect on the utilization of sugar by the

muscles, but a definite effect on the hepatic utilization of sugar. However, its side effects (agranulocytosis and skin rashes) have led to greater use of tolbutamide (or Orinase).

While the full evaluation and understanding of the action of these latter agents is yet to be elucidated, it is known they are ineffective during infections and are not helpful if the daily dosage is over 20 units. It is apparent that they have little or no value in the treatment of the juvenile diabetic. In the older diabetic, when there is insulin insensitivity and obesity, their use as hypoglycemic agents may reduce the need for exogenous insulin by increasing the effectiveness of the insulin (?endogenous).

INSULIN ADMINISTRATION. The initial insulin dosage can be approximated by estimation of the blood sugar. Assuming that sugar is freely miscible, the degree of excess sugar in the blood will be shared by all tissue fluids—roughly two thirds of the body weight in kilograms.

Thus: For a child of 30 kg. the tissue fluid would be 20 kg., or 20 liters. If the blood sugar is found to be 400 mg. per 100 ml., the excess above a normal of 100 mg. would be 300 mg. In 20 liters, this represents a total of 60 gm. of excess sugar. Since a unit of insulin will metabolize 1.5 to 2.0 gm. of sugar, 30 to 40 units would be required. Some sugar may be lost in the urine, and since the dosage is approximate rather than exact, the lower figure of 2 gm. per unit of insulin—or 30 units—would be used.

This calculation has been found to be most helpful. Without a blood sugar determination, or for a small child with the usual sensitivity or response to insulin, the use of this rough formula will avoid the danger of hypoglycemia from overdosage with insulin.

For example: In an infant of 12 kg. the tissue fluid would be 8 liters; in the absence of a blood sugar determination the presence of glycosuria would reflect only an excess sugar somewhere above the renal threshold of 180 mg. per 100 ml., e.g., 200 mg. Because many patients show signs of hypoglycemia at blood sugars of 70 mg., the dosage of insulin should not be greater than would reduce the blood sugar from 200 to 70 mg. per 100 ml., or 130 mg. In 8 liters of tissue fluid this would represent 10.4 gm. of sugar, for which 5 units of insulin would be the safe emergency dosage, until further insulin administration could be determined from blood sugar levels and quantitative loss through the urine.

Hartmann[5] found an initial dose of 2 units of insulin per kilogram to be safe, in the absence of a known blood sugar determination. Since he uses lactate solution simultaneously, there is potential cushioning of the insulin effect by the insulin required to metabolize the potential glucose in the lactate.

In some cases of severe acidosis and dehydration the insulin is administered intravenously with glucose. The use of glucose in diabetic acidosis is controversial. Some authorities claim it is unnecessary and injurious. Our impression is that the endogenous sugar is sometimes not sufficient to combat the acidosis, and that glycogen reserves become exhausted. About half the glucose administered intravenously is

available for metabolism, for which additional insulin may be safely and beneficially given. Even before the days of insulin, intravenous glucose was used (together with normal saline solution or Ringer's solution) with benefit to juvenile diabetics as part of the rehydration program. Slightly hypertonic solutions of glucose aid the establishment of peripheral circulation, the absorption of subcutaneous clyses, and renal function.

As a patient becomes ambulatory, exercise will increase the utilization of carbohydrate and less insulin will be required. This important effect of exercise is to be recognized when the patient returns to his home; a reduction in the amount of insulin should be anticipated with the greater activity. The mildly diabetic child will often show recovery of tolerance during the night, so that morning fasting blood sugar may be in the normal range. Insulin is then required chiefly in relation to meals during the day. Severe diabetics will require a fourth injection of standard insulin during the night. Care must be taken to vary the site of injection in order to prevent subcutaneous changes in fatty tissues, since the insulin is less readily absorbed with the presence of fibrosis.

Diet

Much controversy exists over the proper diet for the diabetic. In the pre-insulin era the amount of carbohydrate was reduced to a minimum.[12] Undernutrition was the rule, particularly for the growing child. Children were often kept on a semi-starvation regimen of thrice-cooked vegetables, diabetic broth and bran wafers. When glycosuria diminished, a low caloric diet was fixed by the minimum protein requirement and a low carbohydrate content. The fat content was adjusted in relation to the ketogenic ratio provided by the remaining calories, which meant a diet comparatively high in fat content. However, as Newburgh and Marsh[13] demonstrated, the diet had considerable scientific justification: The low carbohydrate content and the delayed availability of glucose from the protein and fat of the diet did not suddenly flood the body with glucose. The recovery of some carbohydrate tolerance, and some return of the endogenous insulin, was encouraged by holding hyperglycemia to the minimum; at the same time the fat content was not so excessive as to induce ketosis.

Although most juvenile diabetics of the pre-insulin period died in acidosis or were undernourished and underdeveloped until an infection proved fatal, nonetheless a few survived for surprising lengths of time. At the University of California Clinic there is record of one diabetic who is still alive since his pre-insulin onset.

Though the advent of insulin as a therapeutic agent has altered procedures and prognosis radically, some controversy still exists over the

diet. There is no doubt that the pre-insulin high fat diet was artificial and unpalatable for long, continued use. The restriction and starvation necessitated close observation, both in the hospital and at home, and invariably invited subterfuge and deceptive violation.

Much can be said for the psychological basis of the self-selected diet. However, for regulation of the insulin dosage and the avoidance of marked fluctuations in the blood sugar, some degree of dietary control is desirable. Too low a carbohydrate content may prove unpalatable and restrict the variety of permissible foods; too high a content may cause postprandial hyperglycemia and glycosuria, despite careful insulin dosage. The child's likes and dislikes, and the family and racial preferences of foodstuffs, should be considered so that little discrepancy exists between the family menu and that of the patient. The use of food substitutes with the same carbohydrate content permits a wide variety of foods without jeopardizing the constancy of carbohydrate content. But, whether high or low, the carbohydrate content of the diet should be constant, since it is this element of the diet that determines the dosage of insulin. Protein should be adequate for the growing child, but, as with fat, it has little effect on the insulin requirement. The total calories may vary somewhat, but should be related to the patient's nutritional state.

The caloric requirements are gauged on the basis of the patient's physique (ideal weight for his age and height). If the Wetzel grid is used, the basal caloric need can be correlated with his growth status—his total caloric requirement approximating twice that of the basal metabolism. Protein requirement, which is important for the growing child, is likewise fixed on the basis of his ideal physique. The carbohydrate content, though not high, permits the use of readily available foods. We believe that this degree of restriction of carbohydrate requires less insulin and avoids the more marked fluctuations of blood sugar. The diet, likewise, is not too bulky and is more regularly consumed. Hartmann[5] estimates such a diet will contain approximately 15 per cent of the calories in protein, 35 per cent in carbohydrate, and 50 per cent in fat.

Greater restriction of the diet may be desirable for young diabetic infants. The use of milk formula without added sugar and of lactose-free milk curd will lower the carbohydrate content and, hence, the insulin dosage. Scraped beef, vegetables, fruit and egg can be added as the age requires. For all juvenile diabetics it is best to check the initial diet for its adequacy in protein and total calories. With a fairly fixed amount of carbohydrate, variations can be made in the menu from the list of substitute foods of similar carbohydrate content.

In the rare instances when a low renal threshold for glucose accompanies diabetes mellitus, the diet is adjusted with lower fat and higher

carbohydrate and protein content. Though postprandial glycosuria cannot be prevented, it is quantitatively less than with the higher carbohydrate intake. In such cases the presence of ketonuria is a more reliable guide to insulin dosage than glycosuria.

Continuation Program

All too frequently the clinic and the physician are satisfied to have brought the acutely diabetic child to a degree of control at which his life is not immediately threatened. The less spectacular, but to some extent more important, phase relates to continued advice and planning. Intelligent cooperation on the part of the entire family is necessary for the successful home-care program for the diabetic child.

Acceptance of the diagnosis is essential. Disbelief (Christian Science), protest or parental indifference may lead many to seek easier measures or remedies—even quackery; at the same time the attitude and behavior of the child may be adversely affected. Oversolicitous parents may become too protective and too possessive of the child.

Both the younger and the older diabetic child must be encouraged to share in the responsibility for the condition as they mature. If such cooperation is not encouraged, the diabetic child may express his rebellion against the imposed restraints by hostility toward the parent and/or the doctor, or he may surreptitiously violate the diet or develop compulsive eating habits. As the child grows older, more responsibility should be placed on him. He should know how to administer his own insulin and to vary the site of injection. The deltoid areas and thighs should be used in rotation, since the persistent use of one site can lead to local edema and pseudohypertrophy and, ultimately, to atrophy of the subcutaneous tissue, with fibrosis. While patients may prefer this less sensitive area, the absorption and dosage of insulin is poor and cosmetic disfigurement unfortunate. The older child should be encouraged to test his own urine. His familiarity with equivalent carbohydrate substitutes will enable him to make a fair selection in his menu, whether at home or away, and will prepare him for greater variation of activities as an adult.

Diabetics who initially become accustomed to a weighed diet can quickly translate it into household measures. As adults, they will not continue the use of scales for weighing; but the background of having done so will provide a degree of caution as to the indiscriminate disregard of dietary control. The more the patient shares in the responsibility of his own care, the better the insurance for self-education and his future. At times it becomes the physician's responsibility to see that the mother who initially assumed sole responsibility is persuaded to relinquish some of the program to the child.

After the acute phase of the diabetes, and during recovery of autogenous insulin production, Hartmann[4] has found the use of the total available glucose in the diet a useful guide for the insulin dosage. Total available glucose (TAG) is estimated from the sum of 100 per cent of carbohydrate, 58 per cent of protein, and 10 per cent of the fat in the diet. This sum, less the amount of glucose in the 24-hour urine, will give the amount of glucose metabolized and, when divided by the amount of insulin used, will give some indication of the metabolic efficiency of the insulin for that particular patient.

By the same token, the possibility and desirability of fairly normal activities for the child are emphasized. Too often, family and friends, by attitudes of overprotection and sympathy, promote dependence and semi-invalidism. It is well to tell parents that the handicap of diabetes can be less for the young child who comes under early control than for those who develop diabetes in later life, when adjustment is much more difficult.

The diabetic patient and his parents usually need considerable reassurance, since, initially, they may be overwhelmed by the implications of the diagnosis. Menus, directions for insulin administration, tests for urine, and so forth, should be presented gradually, with opportunity to perform them under supervision in the initial stages. Booklets, such as those published by the Metropolitan Life Insurance Company, are better introductions than the more comprehensive "manuals" to which they may be referred later.

Infections

Infections pose a serious threat to the diabetic; they act as insulin inhibitors or antagonists, and make additional insulin a necessity. If bed rest becomes necessary, there is further increased need for insulin during this period of relative inactivity. Fluid, too, is important, and a liquid diet of fruit juices and/or lactate-lactic acid solution has been used, when possible, in order to avoid parenteral administration. Antibiotics, of course, are of great value for some infections.

Diseased teeth or tonsils should receive early and prompt attention; and there is gratifying benefit when corrective measures are undertaken.

Schooling and Recreational Activities

These are also of concern. The diabetic patient should be encouraged to participate in group activities. It is sometimes necessary to remonstrate with the mother who forbids her son's participation in school athletics. It is important to show that, with spurts of increased exercise, more calories must be given or less insulin administered; in anticipation

of participation in an athletic event, the patient may need to protect himself by an extra snack. Similarly, adjustment of the insulin can be made when a social event is accompanied by refreshments.

There is considerable merit, at present, for the diabetic summer or vacation camp, but ultimately such special and separate group activity should be replaced by participation in more generalized programs.

The long-term program for the diabetic also involves vocational advice. An effort should be made to encourage plans for future constructive occupation. Many diabetic children progress through college, although certain occupations are hazardous. In many communities it

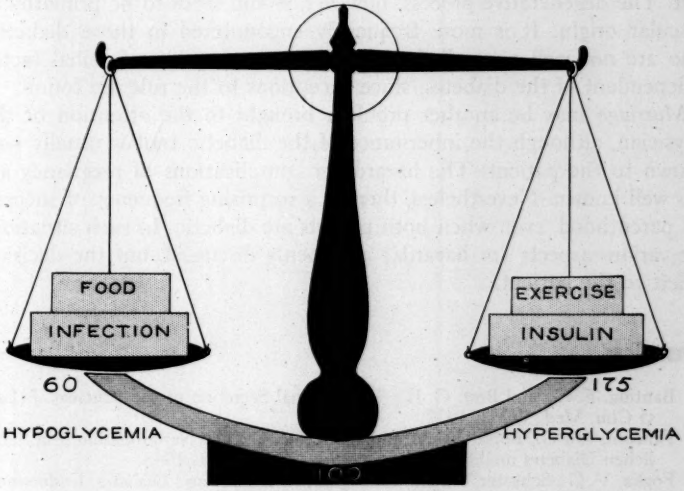

Fig. 1.

may be difficult for a diabetic to get a license to drive a car or to work with certain types of machinery. In case of emergency a diabetic identification card or tag should be carried by all diabetics.

Degeneration

With increasing age the diabetic child requires increasing amounts of insulin, although this increased need is not entirely attributable to the increase in body size. Priscilla White[14] suggested that linear growth, rather than weight, intensifies the diabetic state. Whatever the cause, the juvenile diabetic is subject to more rapid degenerative lesions than is the average child.

Fanconi[2] found that the majority of juvenile diabetics in his group

showed signs of nephropathology (Kimmelsteil-Wilson syndrome) 15 years after the onset of diabetes, and succumbed after 20 to 25 years. Not all clinics, however, share such a pessimistic outlook, and attempts have been made to explain the differences on the degree of control (the Swiss use the self-selected diet) and/or racial and environmental factors peculiar to Switzerland, such as the widespread thyroid deficiency. In most clinics of the United States it is generally believed that the best insurance against degenerative disease in the diabetic is the adequate control of glycosuria and glycemia. At the University of California Clinic the values for the large cholesterol molecule have not been found to be closely correlated with the degree of control or the diet. The degenerative process, however, would seem to be primarily of vascular origin. It is more frequently encountered in those diabetics who are not well controlled, although there may be a familial factor independent of the diabetes, since exceptions to the rule are found.

Marriage may be another problem brought to the attention of the physician, although the inheritance of the diabetic trait is usually well known to the patient. The hazards or complications of pregnancy are less well known. Nevertheless, there is a surprising frequency of successful parenthood, even when both parents are diabetic. In such situations the various aspects (or hazards) are openly discussed, but the decision is left to the patient.

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LONG-TERM EXPERIENCES WITH METHYLTESTOSTERONE AS A GROWTH STIMULANT IN SHORT IMMATURE BOYS

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Recently, Sobel et al.[7] and Wilkins[8] have questioned the use of methyltestosterone as a growth stimulant in short boys because of fear of disproportionate skeletal maturation with resulting impairment of eventual stature. Our data on rates of growth and of skeletal maturation are based on 59 short, retarded boys treated with methyltestosterone and 13 similarly retarded boys treated with methyltestosterone and thyroid substance. These 72 represent all our patients whose original x-ray films are still available and whose treatment was continued for six months or more. The total number of subjects treated since 1938 is 107. Skeletal age assessments from x-ray films taken *before treatment* were available for 51 of the 59 boys treated with methyltestosterone and nine of the 13 boys treated with methyltestosterone and thyroid. Control data were derived from 25 late-maturing boys previously reported by Bayley.[3] In this group complete data were available at all ages reported.

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The two treated groups were retarded to a similar degree before treatment (skeletal age averaged 17.4 months less than chronological age), but they were shorter than the control group, so that the prediction for ultimate height averaged only 66.7 inches, with a standard deviation of 3.9 inches. Treatment consisted of methyltestosterone alone in a daily dose of 5 to 20 mg. in 46 cases and 30 mg. in five additional cases. Thirteen other boys received additional thyroid substance in doses of 15 to 200 mg. a day.

The data are summarized in Tables 1 and 2 and in Figure 2. In Table 1 and Figure 2 the rates of growth are compared for three groups of boys, using the maximal growth age (MGA), the year in which the annual rate of growth was greatest, as a point of reference.[6] The use of an *observed* MGA avoids the errors inherent in the use of estimated "height age" as a standard of reference.[2] The annual gains for the treated boys are all based on growth after treatment was started. The boys were available for observation for varying lengths of time. As will be seen in Table 1, few treated boys failed to attain their maximal growth in the first year of treatment. The curves of increments of the treated boys are similar to those of the untreated controls, despite the younger age at which the artificial puberal spurt was induced.

It is evident from their short stature that the annual rate of growth in these boys before treatment must have been less than normal. From Figure 2 it can be seen that even the few who did not achieve maximal growth in the first year began to grow more rapidly than normal.

By reference to Figure 2 it will be seen that the treated subjects grew at least as rapidly as, and for a longer period than, the untreated boys. It might thus be inferred that their ultimate stature would exceed that which they would have attained if left untreated. We have used the method suggested by Bayer and Bayley[1] for estimating the effect of treatment on adult stature from successive predictions based on skeletal age. By means of the Bayley-Pinneau tables[4] predictions for adult height could be made serially for 27 boys treated with methyltestosterone and for nine boys treated with methyltestosterone and thyroid (Table 2). Before institution of methyltestosterone treatment alone, prediction for adult height of this particular group of boys was 65.9 inches; subsequent to treatment prediction for these same boys was 66.4 inches, certainly no loss in growth potential. That the treatment does not stunt ultimate growth is established in 20 boys who have attained their adult stature, which exceeds the height predicted for them before treatment by 1.1 inches. Serial predictions for the nine boys who received methyltestosterone plus thyroid substance were on the average unchanged after treatment (initial 66.9 inches, subsequent 66.7 inches). These nine boys were all treated at the younger ages (range six to 14 years at initial predictions), and their adult heights are not yet known.

TABLE 1. *Growth in Relation to Year of Maximal Annual Gain (Means)*

	YEARS DEVIATION FROM MAXIMAL GROWTH AGE (MGA)								
	−3 yr.	−2 yr.	−1 yr.	MGA	+1 yr.	+2 yr.	+3 yr.	+4 yr.	+5 yr.
CONTROL (retarded boys)									
Number of cases	25	25	25	25	25	25	25		
Chronologic age (yrs.)	12.5	13.5	14.5	15.5	16.5	17.5	18.5		
Skeletal age (yrs.)	11.8	12.7	13.6	14.4	15.3	16.2	16.7		
Gain (inches)	1.7	2.3	2.5	3.5	1.8	1.0	0.8		
TREATED									
Methyltestosterone									
Number of cases	2	5	15	51	47	47	15	7	3
Chronologic age (yrs.)	12.0	12.8	14.3	14.6	16.1	16.9	18.1	18.7	19.7
Gain (inches)	2.6	2.4	2.9	3.8*	2.4	1.6	0.9	0.6	0.3
Methyltestosterone plus thyroid									
Number of cases	1	4	7	14	8	8	5	4	
Chronologic age (yrs.)	10.5	11.5	13.0	13.0	14.3	15.6	16.8	17.3	
Gain	2.3	2.7	2.7	3.7*	2.6	1.8	1.2	0.8	

* S.D. at MGA is 0.7 inch for both groups of treated boys.

TABLE 2. *Predictions of Adult Stature*

GROUP	BEFORE TREATMENT			AFTER 6 MONTHS OR MORE OF TREATMENT			ADULT STATURE		
	No. of Cases	Age	Prediction	No. of Cases	Age	Prediction	No. of Cases	Mean	S.D.
			Mean S.D.			Mean S.D.			
Controls	25	12.0	70.2	25	15.0	70.1*	25	71.2	2.6
All treated	60	13.7	66.1 3.13						
M-T treated									
Initial prediction	51	14.2	66.1 3.4						
Repeat prediction†	27		65.9 3.8	27		66.4 2.6			
Growth completed†	20	14.2‡	66.4 2.9				20	67.5	2.6
Repeat prediction and growth completed†	9	13.8	65.6 2.9	9	17.9	66.5 2.1	9	65.1	2.3
M-T + thyroid-treated	9	10.7	66.9 1.7	9	13.9	66.7 3.2			

* Untreated, but entered here for comparison at similar age.
† Skeletal age − 11.4.
‡ Skeletal age − 12.6.

S.D. = standard deviation = $\sqrt{\frac{\Sigma d^2}{n(n-1)}}$

Institution of methyltestosterone therapy alone was followed by a prompt spurt of growth in 47 of the 51 boys. The gain for the year of maximal growth averaged 3.8 inches, with a standard deviation of 0.7 inch. That is, approximately two thirds of the boys grew within the limits of 3.1 to 4.5 inches. Genital maturation and weight gain appeared in all cases as the usual androgenic and anabolic effects of methyltestosterone.

As far as adverse effects are concerned, there has been no evidence of damage to fertility in those few boys who have attained sufficient age to be married. At least five are known to be fathers. One serious drawback to methyltestosterone therapy has been adolescent mammo-

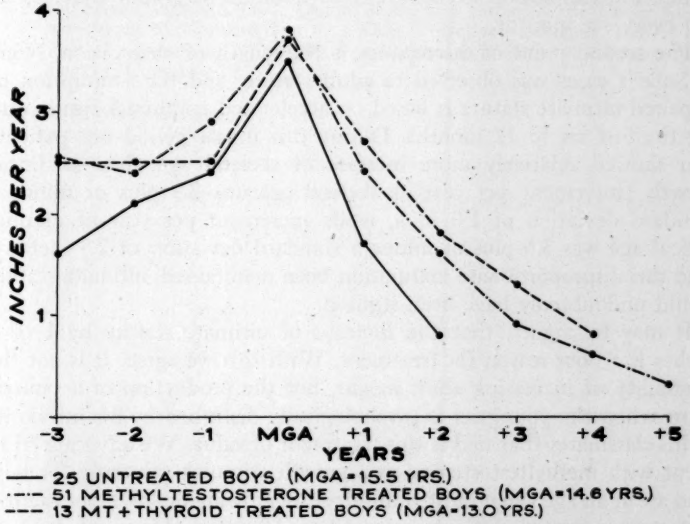

Fig. 2. Annual growth rate of late-maturing boys grouped by maximal growth age (MGA) (year in which annual growth was maximal).

plasia, which occurs so commonly in spontaneous puberty[5] that it might be anticipated in induced puberty. This progressed to gynecomastia requiring simple mastectomy in six cases early in our experience. In the more recent cases reduction of dose or withdrawal of treatment has obviated this complication.

In summary, treatment with methyltestosterone may evoke two types of skeletal response: (1) linear growth and (2) maturation. The average figures for the relatively small doses we have used show no disproportionate skeletal maturation. However, as may be inferred from standard deviations, a few boys attained several inches more and a few several inches less than the heights predicted for them. Sobel's data show that

larger doses may initially produce maturation more rapidly than linear growth. Two points are at issue here: the size of the dose and the duration of observation. In general, both Sobel[7] and Wilkins[8] have used larger doses, often 30 or 40 mg. of methyltestosterone a day. The majority of our patients received only 10 mg. a day. In the few cases in which we used larger amounts we have not consistently seen a relation between dosage and rate of either growth or maturation. Accelerated maturation was observed in one boy who received methyltestosterone, 10 mg., plus thyroid substance, 130 mg. daily, and whose skeletal age matured five years and nine months in three years and nine months, so that the prediction for his adult height fell from 67.1 inches to 64.5 inches. For this reason we believe it advisable to determine the skeletal age every six months.

The second point of discrepancy is the length of observation. None of Sobel's cases was observed to adult stature, and the assumption of impaired ultimate stature is based on accelerated epiphysial fusion during the first six to 12 months. During this initial period our patients also showed relatively more increase of skeletal age than of linear growth (increment per year of skeletal age was 2.5 plus or minus a standard deviation of 1.0 inch, while increment per year of chronological age was 3.6 plus or minus a standard deviation of 2.9 inches). Had this disproportionate maturation been maintained, ultimate stature would undoubtedly have been stunted.

It may be argued that the increase of ultimate stature by 1 or 2 inches is a poor reason for treatment. With this we agree. It is not the possibility of increasing adult height, but the production of a puberal spurt when the youngster is psychologically disturbed by his inferiority to his classmates that makes this treatment of value. We advocate treatment with methyltestosterone as a growth stimulus primarily for boys who are at an age when most youngsters are growing rapidly. Our methyltestosterone-treated patients were 10 to 18 years old, in contrast to Sobel's patients, who were 5½ to 10 years old. Since Sobel has pointed out that small doses seem to promote growth fully as much as larger ones, it is probably advisable to use minimal amounts of methyltestosterone.

EDITOR'S NOTE. There has been much difference of opinion in this problem; most observers feel that growth can only be borrowed and that the ultimate height in adult life is not increased. One of the objectives of the writers was to produce puberal spurt. By careful studies using a smaller dose—10 mg.—than the larger dose of others heretofore, they feel that they have avoided the undesirable increased maturation of epiphyses and the undesirable increased masculinity. They also feel that their "treated subjects grew at least as rapidly as and for a longer period than the untreated boys." . . . "That the treatment does not stunt ultimate growth is established in 20 boys who have attained their adult stature, which exceeded the height predicted for them before treatment by 1.1 inches." They were not trying to increase adult height. This thesis may or may not be agreed upon by other experienced students. W.A.R.

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PROBLEMS OF GENITAL INFANTILISM

Investigation and Treatment

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Genital infantilism ("sexual infantilism" or "hypogonadism") is a diagnosis frequently made by pediatricians and other physicians dealing with children. Yet it is one which is extremely difficult to establish with any degree of certainty in patients within the pediatric age range, since all prepuberal children have sexual infantilism and the age of onset of puberty varies a great deal. Certain hypergonadotropic syndromes can be identified positively in late childhood, however, and in certain well defined syndromes one can predict with a reasonable degree of certainty that sexual maturation will not occur.

There is little justification for being dogmatic in discussing hypogonadism. The mechanisms involved in the control of sexual maturation and growth are understood only superficially. To what extent these mechanisms are dependent upon such vague "non-endocrine" influence as "hereditary genetic patterns" is not known; the endocrine factors involved are better, but not completely, understood. We have only the most meager understanding of the interrelations among the hormones produced by different endocrine glands, of the mechanisms which control formation and release of these hormones, and of the manner in which they produce their effects on the target organs.

Not only is our understanding of mechanisms involved in normal sexual maturation limited, but indeed there is no real understanding of the exact meaning of "normal" and "abnormal" genital development and sexual maturation. There is little consolation for the underdeveloped, sexually immature 17-year old boy in the fact that his condition is termed "delayed maturation" and considered a "normal variant" and

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that he will eventually mature normally. Nor is he much relieved by the knowledge that it is "genetically determined" or a "hereditary pattern of development." To the thinking physician such clichés should not be any more acceptable than they are to the patient. Yet it is not practical or desirable to submit every patient to an extensive endocrine investigation simply because the question of delayed sexual maturation has been raised. Conversely, the physician cannot justifiably pursue a policy of watchful waiting in all cases, but has an obligation to be aware of diagnostic and therapeutic measures which are available for proper management of such problems.

NORMAL SEXUAL MATURATION

The process of normal sexual maturation begins in utero. By the moment of birth it has advanced to such an extent that there are remarkable differences, not only anatomically, but also physiologically and psychologically between the male and the female infant; thereafter these differences become progressively more pronouncd. During the preadolescent period small amounts of both 17-ketosteroids and estrogens are found in the urine of both sexes in approximately equivalent quantities. These appear to arise from the adrenals rather than the gonads. Since their concentrations differ little with sex, it is difficult to understand how they can play an important role in determination of typical sex-specific developmental patterns during the prepuberal period unless genetically determined differences in tissue responsiveness cause the tissues of the male to respond more readily to androgenic stimulation and those of the female to respond more readily to estrogenic stimulation.

Exactly what initiates the onset of puberty is not known. The first recognizable event in this process, however, is activation of the anterior pituitary with regard to secretion of gonadotropins and an increased production of adrenal androgens. These changes may occur at widely varying ages in different children for reasons which are not understood, but seem to bear some relation to other evidences of maturation of tissues, i.e., somatic growth and the development of epiphysial ossification centers. In both the male and the female the various manifestations of sexual maturation usually appear in a predictable sequence; after its initial appearance, however, each secondary sexual manifestation may develop at its own characteristic rate. Therefore there may occur an almost infinite variety of patterns of sexual development in normal persons. Space does not permit a more detailed description of normal variants in sexual developmental patterns, although this is a subject of crucial importance to the physician responsible for the medical care of children. The reader is referred to several excellent

studies[4, 16, 18, 27, 40, 42, 44, 46, 47, 51] and recent summaries[52, 57, 58] for more complete discussion.

ENDOCRINE REGULATION OF GONADAL FUNCTION

In either sex the functions of the central nervous system, the pituitary gland and the gonads are intimately interrelated. Stimulation by pituitary gonadotropic hormones is necessary for activation of the gonads to produce their hormones; and, in turn, it appears that neurologic stimuli are necessary to cause the pituitary to produce gonadotropic hormones. Homeostasis is achieved by virtue of the fact that gonadal hormones or their degradation or conversion products inhibit the release of additional gonadotropic hormones by the pituitary, probably by an effect on the central nervous system. Sexual infantilism thus may be attributable to a functional failure at any of these three levels: central nervous system (probably hypothalamic), pituitary or gonadal.

Figure 3 shows graphically the interrelationships in the hypothalamic-pituitary-gonadal mechanism for control of gonadal function. In the female the pituitary produces three tropic hormones which are directly involved in regulation of ovarian function: the follicle-stimulating hormone (FSH), the luteinizing hormone (LH) and the luteotropic hormone (LTH). These hormones all are essential for controlling the production of the two types of ovarian hormones, estrogens and progestins.*

The primordial ovarian follicle can progress only to the antrum stage independently of pituitary stimulation. Follicle-stimulating hormone alone stimulates follicular maturation only to the stage of the preovulatory follicle. In combination with minute amounts of LH, it stimulates the production of estrogen by the follicle, but does not cause ovulation. When relatively large amounts of LH are present in combination with FSH, ovulation occurs with the formation of the corpus luteum. Luteotropic hormone then stimulates the corpus luteum to produce progestin. Homeostasis is achieved by a complicated mechanism in which estrogen inhibits FSH production and stimulates LH production (and perhaps stimulates LTH production), and, conversely, progestin inhibits LH production.

In the male only two pituitary gonadotropic hormones are known with certainty to be of physiologic significance. Follicle-stimulating hormone stimulates the development of the spermatic tubules and causes spermatogenesis to occur. Luteinizing hormone, which in the

* "Estrogen" refers to all substances which produce growth in the vagina, uterus and mammary glands of castrate or immature female animals. "Progestin" refers to all compounds which produce progestational changes in the female genital tract to prepare the uterus for pregnancy.

male commonly is termed ICSH ("interstitial cell-stimulating hormone"), induces the development of the interstitial cells of Leydig and the production of androgen. As in the female, homeostasis is achieved by virtue of inhibition by gonadal hormones of gonadotropin production. Follicle-stimulating hormone, in addition to stimulating growth of spermatic tubules and spermatogenesis, is thought to stimulate the production by the tubules of a hormone, "inhibin," which inhibits the production of FSH. Interstitial cell-stimulating hormone stimulates the Leydig cells to produce androgens, and the androgens in turn inhibit the production of ICSH. Also, androgens in large quantities inhibit FSH

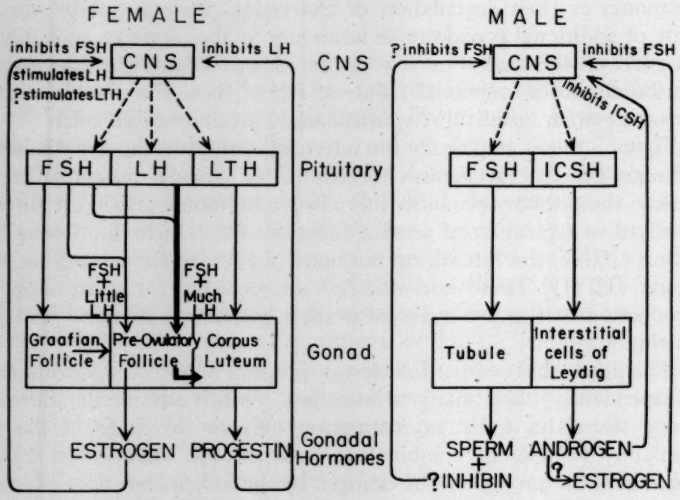

Fig. 3. Endocrine regulation of gonadal function.

production; this effect probably is attributable to the fact that testosterone is metabolized in part to form estrogenic substances.[14]

In addition to the hypothalamic-pituitary-gonadal mechanisms just described, other endocrine mechanisms are of importance in the regulation of gonadal function. Either hyperfunction or hypofunction of the adrenal cortex, of the thyroid or of the pancreatic islet cells can produce delayed sexual maturation.

TYPES OF SEXUAL INFANTILISM

Several different classifications of sexual infantilism have been proposed. Each of these has certain merits which cannot be disregarded, and none is entirely satisfactory. These classifications might be regarded as comprising three groups: etiologic, physiologic and morpho-

logic. Most etiologic classifications that have been advanced subdivide hypogonadism into three main categories, depending upon which of the three members of the hypothalamic-pituitary-gonadal system is involved primarily; each of these main categories, in turn, is subdivided according to the basic etiology. Although this type of classification is less definitive than the morphologic or physiologic classifications, it is probably more useful clinically in patients within the pediatric age range. The etiologic classification of sexual infantilism presented in Table 3 represents but a slight modification of those advanced by previous authors[52, 58] and provides a convenient and useful approach to the systematic consideration of this condition in children.

TABLE 3. *Classification of Sexual Infantilism*

A. HYPOTHALAMIC
   1. Destructive lesions (Froehlich's syndrome)
   2. Congenital defect (Laurence-Moon-Biedl syndrome)
B. PITUITARY
   1. Primary
      a. Generalized pituitary deficiency
      b. Fractional pituitary deficiency
   2. Secondary
      a. Abnormal function of other endocrine glands
         (1) Thyroid: hyperthyroidism or hypothyroidism
         (2) Pancreas: diabetes mellitus
         (3) Adrenal cortex: hyperadrenocorticism or hypoadrenocorticism
      b. Chronic and debilitating disease
         (1) Infectious
         (2) Rheumatic
         (3) Metabolic
         (4) Malignant
      c. Nutritional disturbances
         (1) Obesity
         (2) Undernutrition
         (3) Specific dietary deficiency
C. GONADAL
   1. Gonadal dysgenesis
   2. Castration: disease, radiation, surgery
   3. Arrested development or degeneration of gonads

Physiologic and morphologic classifications are not satisfactory in young children, since the histologic changes and secretion of hormones upon which these classifications are based do not occur normally in this age group. Yet it is important both for prognosis and for therapy to recognize whenever possible those conditions which inevitably, or in all likelihood, will inhibit genital development and result eventually in genital infantilism.

METHODS FOR INVESTIGATION OF GENITAL INFANTILISM

The methods to be used in the study of patients suspected of having genital infantilism depend upon the age and sex of the patient and

the clinical manifestations he presents. They range from careful evaluation of the clinical history and physical examination to the complicated procedures of surgical biopsy or hormone assays. If the physician is aware of the various causes of genital infantilism and the value and limitations of procedures available for its study, he often may be able to establish or eliminate this diagnosis by clinical evaluation and common clinical laboratory procedures without the necessity of resorting to more difficult and complicated studies.

Methods Applicable to Either Sex

Recognition of Syndromes Associated with Genital Infantilism. As indicated previously, genital infantilism is a characteristic feature of several syndromes which can be recognized by their other manifestations early in life. In these instances it is important for the physician to be aware that sexual maturation will not occur or will be delayed.

The early indications of endocrine abnormalities are considerably different in the child from those in the adult. The child is a developing organism, and the rate and sequence of his development are to a considerable extent under endocrine control. Accordingly, the first clinical evidences of endocrine abnormality often are those provided by abnormalities in the child's development. Somatic growth, epiphysial maturation and sexual development are intimately interrelated. In most situations in which there is acceleration or delay in one of these, there is a similar deviation of the others from the expected developmental pattern. Therefore the existence of retarded somatic growth or epiphysial maturation in the young child should alert the physician to the possibility that this child also might be expected to exhibit sexual infantilism or delayed sexual maturation at a later date.

Recognition of Early Puberal Changes. The process of sexual maturation is often slow and prolonged. Alertness in the recognition of the first indications of the onset of puberal changes may serve to shorten by many months, or even years, the period of uncertainty and worry as to whether spontaneous sexual maturation will occur in the child who for some reason has been suspected of having hypogonadism. In some instances it may even forestall a complicated, expensive and fruitless investigation in a child who is already undergoing sexual maturation.

Urinary 17-Ketosteroids. The urinary 17-ketosteroids reflect androgen production not only by the testes, but also by the adrenal cortex. In the young child all the urinary 17-ketosteroids arise from the adrenal cortex; in the older male variable proportions of these steroids are of adrenal origin. Thus the presence of even a normal amount of these steroids in the urine of a male does not necessarily indicate testicular androgen production. Adrenal 17-ketosteroids stimulate the production

of axillary and pubic hair and the development of acne, but ordinarily do not cause development of the penis in the male or the clitoris in the female.

SEX DETERMINATION FROM NUCLEAR MORPHOLOGY.* A new diagnostic technique, based upon sex differences in nuclear morphology of various cells, has recently been developed. Moore, Graham and Barr[36] in 1953 first reported this phenomenon as being of clinical significance. They studied skin biopsy specimens from normal male and female human subjects and found the "sex chromatin mass"† in 69 per cent (range: 52 to 85 per cent) of nuclei in female specimens and only 5 per cent (range: 1 to 14 per cent) of nuclei in male specimens. More recently this technique has been applied to the study of (1) the leukocytes in human blood smears,[6, 12] (2) buccal smears[34, 35] and (3) vaginal smears.[7]‡ Of these, the study of buccal smears has proved the most practical and useful clinical technique in children.

The conditions in which determination of sex by nuclear morphology is of value include true hermaphroditism, female and male pseudohermaphroditism, gonadal dysgenesis and Klinefelter's syndrome. In the true hermaphrodite either male or female nuclear morphology may occur, but the female type is more common; in male and female pseudohermaphrodites the nuclear sex corresponds to the genetic sex; in patients with gonadal dysgenesis either type of chromatin pattern may occur, but the male type predominates; and in Klinefelter's syndrome female, as well as male, nuclear chromatin patterns may occur.

URINARY GONADOTROPINS.§ The gonadotropic material in the urine of nonpregnant human subjects usually has been considered to be FSH. There is much evidence, however, that it also contains LH and perhaps LTH. At present there is no critical evidence indicating whether the urinary gonadotropic material is the same or different in subjects of different sex or of different age. For these reasons Albert[1] favors the term "urinary gonadotropin" to include all gonadotropins in urine of either sex and any age and in all clinical conditions except those in which chorionic gonadotropin is produced.

In studies of urinary gonadotropins most investigators have performed a single assay, thus implying the assumption that urinary gonadotropin excretion is constant. Numerous studies have yielded evidence of great day-to-day variability, however, as well as diurnal fluctuations.

* The reader is urged to consult the excellent recent review by Lennox.[30]

† A small chromatin mass, originally termed the "nuclear satellite," about 1 micron in diameter which occurs near the nucleolus.

‡ This technique has even been applied successfully to determine chromosomal sex of the fetus by study of exfoliative cytology of amniotic fluid.[24, 32, 33, 45]

§ The reader who is interested in details concerning methodology, theory and clinical significance of urinary gonadotropins is referred to the excellent and exhaustive review by Albert.[1]

The excretion of gonadotropins is much greater at night than during the day. Thus those methods which collect night specimens and calculate the 24-hour excretion from this give values which are too high.

Urinary gonadotropins are not detectable in children before the age of puberty. Normal children at and during puberty have positive values similar to those in young adults of both sexes, and the percentage of positive values increases with increasing age. Thus in the young child the urinary gonadotropin determination is of little value in the study of sexual infantilism, since even in the normal child gonadotropins are not present in the urine in detectable amounts. In the person beyond the expected age of puberty, however, the urinary gonadotropin determination is of real value. Heller and Nelson[21] state: "In all instances of hypogonadism there are marked deviations from normal in the output of urinary gonadotropins. Groups with testicular failure invariably show excretion higher than normal. Those with pituitary failure (and secondary testicular failure) invariably show subnormal excretions." On this basis they classify all male hypogonadism as either "hypergonadotropic" or "hypogonadotropic." Howard, Sniffen, Simmons and Albright,[22] on the other hand, include in their classification a third category, "conditions with normal FSH excretion."

From experimental studies real sex differences in pituitary gonadotropin secretion appear evident. The male pituitary secretes gonadotropins at a low and relatively constant rate which is adequate to maintain the integrity of the male genital organs, but would not be adequate to induce luteinization of ovarian follicles in the female.[52] In the normal postmenarcheal female, however, gonadotropin secretion is at a faster rate and varies rhythmically during the menstrual cycle. Thus in evaluation of urinary gonadotropin excretion it is important that assays be done repeatedly before definitive conclusions are drawn about the status of pituitary-gonadal function.

Methods for Investigation of Genital Infantilism in Males

The testis consists of three components: (1) Sertoli cells, (2) germinal epithelium, and (3) Leydig cells. The Sertoli cells afford mechanical support for the germinal epithelium and produce "inhibin," which inhibits release of FSH and stimulates release of ICSH by the pituitary. The germinal epithelium is responsible for spermatogenesis. The interstitial cells of Leydig produce male androgenic hormone, presumably testosterone, when stimulated by ICSH. The latter also stimulates the tubules, as does FSH; testosterone likewise stimulates the tubules, so that this effect of ICSH may be mediated through testosterone.

The evaluation of testicular function, therefore, becomes a matter of

determining whether the testes are producing sperm and whether they are producing androgen or are capable of producing it. The function of the testicular tubules is evaluated by (1) testicular size, (2) urinary gonadotropin, (3) testicular biopsy, and (4) examination for sperm. The function of the interstitial cells is evaluated by (1) examination of the penis, scrotum and prostate, (2) urinary 17-ketosteroids, (3) testicular biopsy, and (4) response to chorionic gonadotropin.

Testicular Biopsy.* Leydig cells are present in the fetal testis (probably as a reflection of maternal chorionic gonadotropin), but disappear completely usually within a week or two and certainly by five months after birth. Thereafter the testis remains in a quiescent state until puberty. The tubular tissue does change progressively, however, toward maturity; there is some growth of the testis as a whole, slight mitotic activity occurs, and primitive spermatogonia become recognizable in the germinal syncytium. The earliest puberal change observed by Albert et al.[2] has been in a nine-year old boy; usually these changes occur later. Tubular stimulation appears to occur first and is manifested by increase in size and tortuosity of the tubules, the differentiation of Sertoli cells, and the gradual development of a mature seminiferous epithelium. These changes occur before the development of Leydig cells.

Before puberty testicular biopsy is of little value in the study of hypogonadism. It is possible to determine grossly whether a testis has developed to below the six-year level or to between six years and puberty, but this differentiation cannot be made with certainty. The significance of an apparent delay in testicular development during the prepuberal period with regard to eventual prognosis for testicular maturation is not known.

After the age of puberty testicular biopsy becomes perhaps the most important technique for evaluation of testicular function. Usually testicular biopsy alone in conjunction with careful clinical evaluation of the patient will provide all the information necessary for the proper management of hypogonadism in the male. Albert et al.[2] have proposed a morphologic classification of hypogonadism which divides all known testicular disease into four categories: (1) mature, recognizable Leydig cells are absent or atrophic; (2) mature Leydig cells are present; (3) both tubules and Leydig cells are abnormal; (4) mixtures of two or more of (1), (2) and (3). These major categories are subdivided on the basis of clinical features and of other histologic characteristics of the biopsy. This classification, which relegates etiologic diagnosis to a subordinate position, is valuable for use in adult patients since it

* Those interested in details concerning histology of the normal testis throughout the life-span of man and results of testicular biopsy in various forms of male hypogonadism should read the series of papers by Albert and co-workers.[2]

provides definitive diagnosis rapidly and is flexible enough to include all known forms of male hypogonadism. However, because of the immaturity of the prepuberal testis it is not satisfactory for general use in pediatrics.

Chorionic Gonadotropin Test. This test is designed to determine whether the patient is capable of producing androgens. Chorionic gonadotropin is given intramuscularly in a dose of 1000 I.U. three to five times a week for six to 10 weeks. If the testicular interstitial cells are intact, they will respond to this stimulation by production of androgen, and distinct penile and scrotal development will occur. Heller and Nelson[21] proposed a classification dividing all male hypogonadism into eight categories based upon the results of this test combined with the results of urinary gonadotropin assay. Although this classification represents a distinct advance in the consideration of male hypogonadism in the adult, it is of little value in the prepuberal child. The method also has the disadvantage of being time-consuming and involving complicated laboratory procedures.

Methods for Investigation of Genital Infantilism in Females[52, 58]

Ovarian insufficiency is manifested by failure of the ovaries to produce one or both of the ovarian hormones, estrogens and progestins. Adequacy of ovarian function with regard to estrogen formation may be evaluated by (1) physical examination for adequacy of female secondary sexual development, (2) determination of pH of vaginal secretion (becomes alkaline in the presence of adequate estrogen), (3) microscopic examination of unstained urinary sediment for cornified epithelial cells, (4) microscopic examination of the stained vaginal smear for evidence of cornification of vaginal epithelium, (5) "medical" dilatation and curettage, (6) measurement of urinary estrogens, and (7) endometrial biopsy.

The clinical effects of progestin deficiency are less obvious than those of estrogen deficiency and are not detectable by physical examination, since the only known function of progesterone is to prepare the uterus for pregnancy. It is seldom necessary to evaluate ovarian function with regard to progestin production in childhood disorders. When this does seem necessary, however, it can be accomplished by (1) measurement of basal temperature curve, (2) measurement of urinary pregnanediol excretion, and (3) endometrial biopsy.

Urinary Estrogen Determination. Accurate determinations of urinary estrogens would be of great value in studying female hypogonadism. Unfortunately the procedures available for this determination are either so nonspecific as to be of questionable value or are technically difficult to perform. It is to be hoped that those investigators working

with recent innovations in technique (i.e., countercurrent distribution, and so on) will soon be successful in establishing methods of greater clinical usefulness.

"Medical" Dilatation and Curettage. This technique depends upon the fact that progesterone in the absence of estrogen produces almost no physiologic effect. If 5 mg. of progesterone are given daily intramuscularly for five days and then administration is discontinued, menstrual bleeding should occur within 10 days after the last injection. Failure of such bleeding to occur indicates severe estrogen deficiency.

Urinary Pregnanediol Determination. Pregnanediol is formed by the metabolism of progesterone and normally is not present in any significant amount in human urine except during one phase of the menstrual cycle; it abruptly appears within a day or two after ovulation, reaches peak excretion a few days later, and disappears a day or two before menstruation occurs. If this period of increased pregnanediol excretion fails to appear, it indicates that an anovulatory cycle has occurred. The determination of urinary pregnanediol is relatively simple as compared with estrogen determination. Several satisfactory methods have been developed. In this laboratory the method of Bongiovanni and Clayton[5] is used.

Endometrial Biopsy. This procedure is seldom necessary in the study of ovarian function in children. It is capable of giving information about both types of ovarian hormones. If the endometrium is well developed, it indicates that an adequate amount of estrogen is being supplied. Definite secretory changes present in an endometrial biopsy specimen taken just at the onset of menstrual flow indicate that adequate progesterone is present.

CLINICAL FEATURES AND THERAPY OF GENITAL INFANTILISM

Hypothalamic Infantilism

Genital infantilism of hypothalamic type may result from either destructive lesions or congenital defects of the central nervous system. In either case sexual maturation fails to occur because the hypothalamus fails to stimulate the pituitary to release gonadotropins. Clinically, genital infantilism of hypothalamic origin is similar to that resulting from generalized pituitary insufficiency.

Froehlich's Syndrome. The syndrome originally described by Froehlich in 1901 consisted in sexual infantilism, obesity, growth retardation, diabetes insipidus and signs of a tumor in the hypothalamic region. This syndrome may be produced by craniopharyngioma, glioma or any other space-occupying lesion involving the hypothalamus or optic chiasm. The symptom complex described by Froehlich need not be

present in its entirety; patients with sexual infantilism and hypothalamic lesion may fail to exhibit any one or all of the other components of the syndrome. Thus these patients may have no evidence of somnolence, temperature instability or diabetes insipidus; they may have no obesity; and they may be of average height or even tall and eunuchoid in stature.

The common error about this syndrome has been overdiagnosis. There has been a tendency on the part of clinicians to consider this to be the diagnosis in a great many otherwise normal boys who are somewhat delayed in the onset of puberty and have distribution of adipose tissue and perhaps certain other characteristics considered typical of those in patients with hypothalamic lesions. Froehlich's syndrome is an extremely rare disorder and carries the connotation of serious central nervous system involvement. Therefore it should never be made in the absence of definitive evidence for the existence of the central nervous system lesion.

Initial therapy must be directed toward correction of this lesion. If this initial objective is achieved, additional therapy similar to that for primary pituitary deficiency should be instituted.

THE LAURENCE-MOON-BIEDL SYNDROME. This syndrome results from a congenital defect of the hypothalamus. In its complete form it consists in sexual infantilism, obesity, stunted growth, mental deficiency, retinitis pigmentosa, diabetes insipidus, polydactylism and syndactylism. Any one of these features may be absent, including the sexual infantilism. Therefore, if this diagnosis is made in infancy or early childhood, it can be predicted with some but not complete assurance that sexual maturation will fail to occur. Because of the mental deficiency and other congenital anomalies associated with this syndrome, it seems wise to withhold any therapy directed toward correcting the hypogonadism.

Pituitary Infantilism

Genital infantilism may result from either primary or secondary pituitary hypofunction. In either type there is failure to produce gonadotropins in sufficient quantity to provide adequate stimulation for normal gonadal development. Primary pituitary infantilism may result from either generalized or fractional pituitary deficiency. In the former there is inadequate production of all the pituitary tropic hormones; in the latter there is inadequate production of pituitary gonadotropins, and this may or may not be associated with inadequate production of growth hormone or other pituitary hormones.

PRIMARY PITUITARY INFANTILISM. Generalized primary pituitary hypofunction (panhypopituitarism, pituitary dwarfism) is a relatively rare condition which is suspected or diagnosed more frequently than it occurs. This diagnosis should not be made in the absence of convincing

evidence not only of retarded somatic and epiphysial development, but also of thyroid and adrenocortical hypofunction. The pituitary hypofunction usually is idiopathic in origin, but may result from a destructive lesion of the pituitary such as tumor, infarct, hemorrhage or infection; diagnostic study of these patients always should include a search for evidence of such organic lesions. Differentiation of panhypopituitarism from primordial dwarfism or delayed adolescence is often difficult; with increasing age this differential diagnosis becomes progressively easier to make. Sexual infantilism persists indefinitely; the gonads do not mature and secondary sexual characteristics fail to develop. Urinary excretions of gonadotropic hormone and of 17-ketosteroids remain unusually low. These patients are insulin-sensitive and may exhibit spontaneous hypoglycemia. These findings, combined with laboratory and/or clinical evidence of hypothyroidism and hypoadrenocorticism, provide strong evidence for the diagnosis of pituitary dwarfism. Ideal therapy would consist in administering the pituitary hormones which are deficient in these patients; since this is impractical, however, the best available alternative is to administer substitution therapy with the hormones of the target glands.

Fractional primary pituitary deficiency may be manifested as less severe deficiency of all or several pituitary hormones or as a specific deficiency of pituitary gonadotropins without deficiency of any other pituitary hormone. Such patients may have any degree of hypogonadism, but nearly always have more evidence of sexual maturation than do patients with panhypopituitarism. Because adrenal androgen production is normal, females may have nearly normal amounts and distribution of sexual hair. Males, on the other hand, tend to have rather scanty sexual hair of female distribution.

Secondary Pituitary Infantilism. Pituitary hypofunction may and often does occur as a result of some other primary disorder. Among the causes of such pituitary dysfunction are abnormal function of other endocrine glands (hyperthyroidism or hypothyroidism, diabetes mellitus, hyperadrenocorticism or hypoadrenocorticism); chronic and debilitating disease (infectious, rheumatic, metabolic, malignant); and nutritional disturbances (obesity, undernutrition, specific dietary deficiency). Therapy in any of these conditions should be directed toward correction of the underlying abnormality.

Gonadal Infantilism

Primary gonadal infantilism occurs in patients with gonadal dysgenesis; castration by surgery, radiation or illness; or arrested development or degeneration of gonads. An important feature differentiating these conditions from primary pituitary or hypothalamic infantilism is the

excretion of increased amounts of urinary gonadotropin; FSH secretion does not begin until approximately the age of expected puberty, so that measurement of urinary gonadotropins before this age is usually not helpful in diagnosis.

GONADAL DYSGENESIS. This syndrome, designated "ovarian agenesis," "Turner's syndrome," "ovarian dwarfism," "syndrome of rudimentary ovaries" or "primary ovarian insufficiency with decreased stature," was first reported as a clinical entity by Turner in 1938;[53] since that time it has been found to occur with sufficient frequency that most major pediatric or endocrine clinics have several examples of it among their clientele. The common feature of all cases is failure of gonadal development in apparent females. The tubes and uterus are infantile, but normally formed; the ovaries appear only as a narrow white ridge in each broad ligament and contain no epithelial or germ cells. No estrogen is produced, but these patients do produce 17-ketosteroids in only moderately decreased amounts. Consequently the secondary sex organs remain infantile, but sexual hair develops, although it may be somewhat sparse and not appear until 14 to 16 years of age. These patients usually have a masculine configuration of the chest and trunk with small nipples situated far apart on a broad thorax.

Associated congenital anomalies are frequently present, and moderate stunting of growth occurs. Epiphysial maturation usually is not more than slightly delayed, however. Even during the first year of life these patients may begin to appear short and broad in stature, and they usually attain eventually a height of only 50 to 58 inches. The congenital anomalies frequently found in association with gonadal dysgenesis include webbed neck, coarctation of the aorta or other types of congenital heart disease, cubitus valgus, unexplained hypertension, and occasionally mental retardation, congenital deafness, various ocular abnormalities, spina bifida, fusion of cervical vertebrae, horseshoe kidney and other deformities. The Bonnevie-Ullrich syndrome (webbing of the neck and congenital lymphedema) is commonly associated with gonadal dysgenesis.[38, 55]

Experimental studies in animals[28, 41] demonstrated that early removal or destruction of fetal gonads results in the development of female genitals. Recent studies indicate that many persons with gonadal dysgenesis (even a preponderance of them) have male chromatin patterns. It appears likely from these observations that failure of embryonic gonadal development due to early injury to the embryo or other cause results in female sexual differentiation regardless of genetic sex.* The occurrence of male chromatin patterns in a high percentage of patients

* A few patients have been reported with some degree of masculinization of the external genitals.[17, 20] It has been suggested[20] that these be termed "gonadal dysgenesis with phallic enlargement.'

with gonadal dysgenesis is extremely useful diagnostically. This test should be performed in any patient who has infantile female secondary sexual organs in combination with developing sexual hair, stunted growth, the Bonnevie-Ullrich Syndrome, or any of the congenital anomalies which commonly occur in association with gonadal dysgenesis. A male chromatin pattern in such patients is nearly diagnostic of gonadal dysgenesis. The only other conditions in which apparent females have male chromatin patterns, true hermaphroditism and the feminizing testicular syndrome, are extremely rare, and neither of these is associated with congenital anomalies or short stature.

With careful clinical observation and intelligent use of available laboratory techniques it should be possible to diagnose most cases of gonadal dysgenesis without resorting to laparotomy and often to make this diagnosis in the infant or young child. It is important to make the diagnosis as early as possible for purposes of prognosis and to prevent the use of various forms of useless or even harmful therapy before the usual time of puberty. At that time estrogen substitution therapy should be instituted to induce maturation of secondary sexual characteristics.

CASTRATION. Prepuberal castrates grow normally during childhood. They often develop into tall, eunuchoid adults, but may attain normal adult size and proportions. If castration occurs before puberty, sexual hair develops, but other secondary sexual characteristics do not. Substitution therapy with gonadal hormones should be given in patients who have reached the usual age of puberty.

ARRESTED DEVELOPMENT OR DEGENERATION OF GONADS. A few instances have been reported[58] in which there was sexual infantilism in females with pubic hair, as in gonadal dysgenesis, but the ovaries showed evidence of arrest at a more advanced stage since they contained nests of epithelial cells and in one case even some primordial follicles with ova. Similar clinical characteristics were described by Albright, Smith and Fraser[3] in two patients that they considered to have "premenarchial menopause." The authors suggest that these patients had developed normally until near menarche and then had experienced menopause. Estrogen substitution therapy is required in both these types of patients.

In males a variety of syndromes due to arrested development or degeneration of gonads has been reported.[48] The best-defined and apparently most common of these is the Klinefelter syndrome.[29] In this condition the interstitial cells of Leydig are present in normal numbers, but are clumped and abnormal in appearance; the tubules are degenerated or hyalinized, with almost complete absence of both Sertoli cells and germinal epithelium. Patients with this syndrome have well developed secondary sexual characteristics and may have normal libido; the

testes, however, remain of prepuberal size, and the patients have azoospermia. Urinary gonadotropins are always elevated; urinary 17-ketosteroid excretion is normal or moderately reduced. These patients may be either tall and eunuchoid or obese with fat distribution similar to that in Froehlich's syndrome, and many of them have gynecomastia. Indicated therapy for Klinefelter's syndrome depends upon the manifestations in the individual patient. Occasionally androgen substitution therapy is indicated. The gynecomastia can be treated effectively only by mastectomy; this should be performed in those patients in whom the gynecomastia causes undue embarrassment or psychologic trauma.

A similar syndrome is that reported by del Castillo, Trabucco and de la Balze[9] as a "syndrome produced by absence of the germinal epithelium without impairment of the Sertoli or Leydig cells" and termed "testicular dysgenesis" by Wilkins.[58] These patients have normal masculine habitus, libido and secondary sexual development except for testes, which remain of prepuberal size and azoospermic. Testicular biopsy reveals Leydig cells present in large clumps and tubules which are composed solely of Sertoli cells, germinal epithelium being absent. The original cases were reported to have normal urinary FSH, but other investigators have found FSH to be elevated in similar patients. Urinary 17-ketosteroid excretion is normal or moderately reduced. Usually no therapy is required.

More recently, del Castillo, Trabucco and Onativia[10] have described a syndrome characterized by complete absence of Leydig cells, germinal maturation arrested at the phase of spermatogonia, and intact Sertoli cells. These patients had eunuchoid habitus, poorly developed secondary sexual characteristics without gynecomastia, decreased libido, azoospermia, and decreased excretion of 17-ketosteroids and urinary gonadotropins. Androgen substitution therapy seems indicated.

Sohval and Soffer[49] have reported a syndrome which resembles both gonadal dysgenesis and Klinefelter's syndrome. They designate this as "congenital familial testicular deficiency." Their patients, two brothers, had small testes, aspermatogenesis, gynecomastia, mental deficiency, diabetes mellitus, multiple congenital anomalies, decreased 17-ketosteroid excretion, and increased urinary gonadotropin excretion. Testicular biopsy revealed the seminiferous tubules to be involved either by true germinal aplasia or by complete fibrosis and hyalinization.

"Turner's syndrome in males" has been reported by several authors.[11, 13, 25, 39, 49, 50] All these patients had congenital anomalies similar to those in patients with true gonadal dysgenesis, but each falls short of being a verified male counterpart of ovarian agenesis in that histologic examination of the testes often was not reported and increased urinary gonadotropins not demonstrated. According to present concepts, the only patients who truly represent the male counterpart

of ovarian agenesis are those with gonadal dysgenesis and male chromatin patterns.

CRYPTORCHIDISM

Whether this subject should be included in a discussion of genital infantilism is debatable. Ordinarily there is no evidence of any endocrine disorder in patients with cryptorchidism; occasionally it may occur in association with pituitary deficiency or primary testicular defects. If there is no associated endocrine disorder, the prognosis for normal masculinization of the patient is excellent; in patients with unilateral cryptorchidism the prognosis for normal spermatogenesis and fertility also is good, but it must be guarded in those with bilateral involvement. There is, however, little evidence to indicate any impairment of fertility in those patients whose testes eventually descend spontaneously. This is important, since in most cases spontaneous descent does occur. It has been reported that the testes are undescended in 10 per cent of male newborns;[37] the incidence of undescended testis has been estimated[31] to be 1 in 25 to 30 in boys under 14 years of age, but only 1 in 400 in men over 21 years.

The evidence is not convincing that early orchiopexy improves the prognosis for fertility.[15] Although Gross and Jewett[19] report 79 per cent fertility following orchiopexy in patients with bilateral cryptorchidism, Johnson[26] had observed equally good results in a large series of untreated patients; spontaneous descent was observed in several patients in this series as late as the sixteenth year of life. Unless someone demonstrates superior results from orchiopexy more convincingly than has been done to date, it would seem that operation should be delayed until approximately this age or until it becomes apparent that the testes will not descend spontaneously, unless operation is indicated by some associated condition. There is general agreement that endocrine therapy will cause descent only of those testes which eventually would descend spontaneously. There is probably no indication for such therapy except as a diagnostic test evaluating the need for surgery.

In pseudocryptorchidism the testes are in the scrotum only intermittently. Since spontaneous descent always occurs in these patients at the time of puberty, no therapy is indicated.

SUMMARY OF SUGGESTED THERAPY IN GENITAL INFANTILISM

Table 4 summarizes the therapy which has been suggested for the most common types of genital infantilism. Space does not permit detailed consideration of dose schedules and therapeutic regimens. These are readily available in standard textbooks of pediatric endocrinology.[52, 58]

TABLE 4. *Summary of Suggested Therapy in Genital Infantilism*

DIAGNOSIS	SUGGESTED THERAPY*
Froehlich's syndrome	Correction of C.N.S. lesion. If successful, gonadal hormone substitution therapy
Laurence-Moon-Biedl syndrome	Therapy for hypogonadism contraindicated by mental retardation and congenital anomalies
Primary pituitary infantilism	Substitution therapy for endocrine deficiencies: thyroid, adrenocortical and gonadal
Secondary pituitary infantilism	Correction of underlying condition
Gonadal dysgenesis	Surgical repair of congenital heart lesions and other congenital abnormalities if possible. Withhold endocrine therapy until age of expected puberty. Then estrogen substitution therapy
Castration	Gonadal hormone substitution therapy at age of expected puberty
Arrested development or degeneration of ovaries	Estrogen substitution therapy at age of expected puberty
Klinefelter's syndrome	Depends on manifestations in individual patient. Androgen substitution therapy if needed. Mastectomy, if gynecomastia is disturbing to patient
"Testicular dysgenesis" del Castillo type	No therapy required
Cryptorchidism	Withhold surgery until age 16 years (?) unless it is indicated by some associated abnormality

* *Gonadal hormone substitution therapy:* In the male, this can be given as methyltestosterone by mouth. Small doses (10 mg. per day) usually will produce gradual masculinization, a spurt in growth, and moderate acceleration of epiphysial maturation. If growth is nearly adequate at the time of initiating therapy, larger doses (30 mg. per day or more) should be used to induce more rapid masculinization and epiphysial maturation. In the female diethyl stilbestrol (1 mg. daily) should be administered to induce development of female secondary sex characteristics. After adequate breast and genital development has been attained (several months) it is desirable to administer estrogens cyclically to induce periodic bleeding. In some instances it may be necessary to administer methyltestosterone daily with the estrogen to provide adequate stimulation for somatic growth and growth of sexual hair or a progestin cyclically to more closely simulate normal menstruation. In either sex it may be necessary to continue substitution therapy indefinitely to avoid loss of the beneficial result obtained.

SUMMARY

The diagnosis of hypogonadism should be made with caution in pediatric patients. During the first few years of life this diagnosis can be made only by recognition of standard syndromes with which it is known to occur consistently; even in the older pediatric patients it must be

made cautiously because of the extreme variability in patterns of normal sexual development and the consequent difficulty in differentiating hypogonadism from delayed normal maturation. When, however, the diagnosis can be established, it is important that this be done in order to determine prognosis and permit a rational approach to therapy. In general, conservative therapy is to be preferred; however, in some instances it is urgent that definitive therapy be instituted without delay.

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GOITROUS HYPOTHYROIDISM

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Goitrous hypothyroidism is a type of hereditary hypothyroidism probably governed by an autosomal recessive gene; it appears in siblings and can recur in succeeding generations. The hypothyroidism, which may be moderate, but more often is excessive, usually precedes the appearance of goiter. The goiter often shows some hyperplastic tissue and adenomas, and areas of atypical neoplasia may develop. The deficit of thyroid hormone production calls forth extra production of thyrotropic hormone and results in a goiter. The congenital absence of the enzymes oxidase and deiodinase (the latter demonstrated by Roche et al.[22]), and mechanisms for normal coupling of iodotyrosines for the formation of thyroxin is thought to be the explanation. There are probably other known cases, and studies on more than 80 cases of goitrous cretinism (mostly children) have been recorded; in nonendemic areas the condition may be more frequent.

This entity has been recognized for centuries, but has been particularly studied clinically since 1870. In the United States goitrous cretinism was first described clinically by Sir William Osler[17] in 1897. Hamilton, Soley, Reilly and Eichorn[8] reported two such children in 1943, and were the first to report the use of I^{131} in children. These two cases had high thyroid uptakes of I^{131}, as in hyperthyroidism, and thyroid biopsies showed hyperplasia. Subsequent studies and case reports were contributed from 1945 to 1957.[1-6, 9-16, 19, 23-30, 32, 33] Informative reports are those of Lerman et al.,[14] Hurxthal and Musulin,[11] Stanbury et al.,[25, 26] Hubble,[10] McGirr and Hutchinson,[16] Costa et al.,[3] Wilkins et al.,[32] and Hayles et al.[9] Goitrous hypothyroidism, which may be the same entity as endemic goitrous cretinism, is sporadic in the United

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States. It is more common in other areas of the world, with or without goiter, where goiter and cretinism are endemic.

The etiological distinction between goitrous cretinism and endemic cretinism is difficult to make. Warkany* states that ". . . I am not willing to say that genetic factors play an important role in the etiology of endemic cretinism. . . ." "There are at least two types of goitrous cretinism. One type, probably genetically determined, occurs in non-endemic areas and is probably due to an inborn inability to synthesize the thyroid hormone in the presence of iodine. The second kind is the endemic cretinism." Warkany and the writer in personal discussions feel that this may well be caused by iodine deficiency, and possibly other factors should also be considered—for instance, goitrogens. Eugster,[7] after studying 204 cretins and their blood relatives, did not think that iodine deficiency was the main cause of goiter. He stated: "Endemic cretinism cannot be a truly hereditary disease."

ETIOLOGY

Goitrous hypothyroidism is due to an inborn metabolic error, probably governed by a recessive autosomal gene. The transmission by both parents or sex-linkage has not been described; the writer did not find any reports of twins being afflicted, though it could occur in them. Stanbury and Querido[27] state that this "hypothyreosis or cretinism could result from enzymatic failure at any step in hormone synthesis or release. . . ."

Since goitrous hypothyroidism occurs in many areas where there is a normal supply of iodine, it does not seem likely that a deficiency of iodine supply could be a primary cause, but it may be contributory. Reilly et al.[19a, 20] have evidence of stable iodine deficiency in such patients as follows: decreased amounts in the plasma, urine, extrathyroidal pool and space; the thyroid gland uptake is increased, however. This would suggest that the thyroid gland keeps the blood and extrathyroidal pool of stable iodine low, resulting in a form of iodine poverty. Faulty absorption of iodine from the bowel does not seem to be the explanation; stool and urine measurements (Table 5, A.T. and K.T.) did not show excessive output.

Stanbury and Querido[27] stated that iodine deficiency is the cause of both goiter and endemic cretinism. Costa† disagreed and thought that endemic cretinism is a typical constitutional disease. Costa suggested that "alterations in iodine metabolism . . . in endemic cretinism, are usually the consequence of, rather than the cause of, the goitrous process." Stanbury and Querido[27a] replied: "Perhaps the most compelling argument in

* J. Warkany: Personal communication.

† A. Costa: *J. Clin. Endocrinol. & Metab.*, 17:801, 1957.

TABLE 5

NAME NO. SEX	AGE OF ONSET—YRS. Hypothyroidism	Goiter	FAMILY HISTORY	I^{131} UPTAKE (YRS.)	PATHOLOGY	START OF THERAPY AGE—YR.	MOST RECENT I. Q. AT YR.	CONVERSION TO PBI^{131} (Ref. 21)	AUTORADIOGRAMS	COMMENTS
A. T. 219722 M	? About 1–2	2	+K. T., sister	High, ‡ 6½	Not done	5½ and 6½	90—8½	Incr.	I^{-}, T-1 and/or T-2, T-4	Hypothyroidism mild; good mentality retained; thyroid size became normal
K. T. 219720 F	? Before 15 mo.	1½	+A. T., brother	High, 4¾	Not done	2½ and 4¾	71—6¾	Incr.	I^{-}, T-4 ? T-1 and/or T-2	More retarded height, bone age, and IQ; goiter disappeared
A. H. 151730 F	? Before 1 yr.	2½	+P. H., sister and aunt	High, 9	Not done	5½	79—10¾	Incr.	I^{-}, T-1 and/or T-2, T-4	Mild skin and hair changes; goiter disappeared after 5 mos.
P. H. 46210 F	? 3–6 mo.	6 mo.	+A. H. and aunt	High, 6	Hyperplasia 6 yr.; inactivity and atrophy	4½	75—4½ 101—19	Incr.	I^{-}, T-1 and/or T-2, T-4	Goiter receded slowly; mentality improved quickly (Fig. 4)
J. S. 61107 M	Shortly after birth	11	+Maternal grandmother needs thyroid extract for goiter	1%, 5 mo. High, 11	At 11½ multiple adenomas; papillary projections; atypical atrophy	5 mo.	Average at 14			Goiter developed during adequate therapy
A. D. 63727 M	Infancy ? 3–12 mo.	? None at 19	No other known cases	High, 19	Involuted thyroid 19 yr.; (? atrophy); papillary projections and infolding	12	48—19			See Fig. 5
L. G.* 196261 F	1–2	3	+3 sisters have goiter	High, 44	Adenomas 44 yr.; Hurthle cells	14	Very retarded mentally			Nervousness for years while on thyroid; aet. 44, ht. 55″; all epiphyses fused (Fig. 6)
B. D.†	? At birth	None aet. 8¾	None	90%, 8 KSCN test neg.	Not done (ref. 32)	8¾	72—8¾	Incr.	I^{-}, T-1 and/or T-2, T-4	Markedly dwarfed; 39″, bone age 18 mos. at 8¾ yr.

* Patient of M. J. Nyda, M.D., San Francisco.
† Patient of M. J. Whitelaw, M.D., San Francisco.
‡ "High," as in hyperthyroidism.

favor of a deficiency of iodine as the causative factor in endemic cretinism is the remarkable disappearance of the disease when adequate methods of iodine prophylaxis are introduced." "We cannot believe that the present facts warrant the exclusion of iodide deficiency as the sole cause of endemic cretinism."

PATHOLOGY

Pathological Physiology

At present the concept of Stanbury and Querido[27] of an inborn metabolic error as the cause of goitrous hypothyroidism is a most plausible one. From the initial trapping of iodine to the final release of hormone, all steps are probably enzymatically controlled. The formation and release of hormone probably depend on the rate at each step. The deficiency or absence of the various enzymes is controlled by autosomal recessive nonsex-linked inheritance laws.

Stanbury and Querido[27] described a type A, due to failure of organification of iodine. Though the absence of an oxidase in the gland is postulated, it has not been demonstrated. Thiocyanate (KSCN) administration to this type empties the thyroid of iodine only; no organified (iodinated tyrosine and thyronine) iodine is formed, and none is detectable in the thyroid, plasma or urine.

Their second type, B, is a failure, for some unknown reason, of coupling of iodotyrosine groups. Normally, two molecules of diiodotyrosine (T-2) couple to form thyroxin (T-4), which is tetraiodothyronine; two molecules of monoiodotyrosine (T-1) couple to form 3-3′ diiodotyrosine; 3-5-3′ and 3-3′5 triiodothyronine (T-3) result from a coupling of one molecule each of T-1 and T-2. Chromatography of the peripheral blood shows that little thyroxin is released, and the gland shows large amounts of mono- and diiodotyrosine. The normal, rapid enzymatically controlled coupling may be slowed or may fail entirely. The author suggests that if the coupling is slowed, even a little, enough normal hormone may be generated so that only partial hypothyroidism results. If coupling has completely failed, deficiency and goiter soon follow.

The third metabolic error (type C) is the failure of deiodination of iodothyronines due to a deiodinase deficiency. A protease which is normally present in the thyroid proteolyzes thyroglobulin and releases triiodothyronine and thyroxin. Roche et al.[22] discovered a specific deiodinase for mono- (T-1) and diiodotyrosine (T-2) in the thyroid and, in lesser amounts, in the liver, intestines and kidney; this deiodinase does not deiodinate triiodothyronine (T-3) or thyroxin (T-4). In euthyroidism, T-1 and T-2 in the thyroid do not appear in the plasma; deiodination of T-1 can occur to a lesser intensity in the other tissues.

It is possible that another deiodinase, not yet demonstrated, deiodinates T-4 and T-3 in the peripheral tissues.

Stanbury and Querido[27] demonstrated T-1 and T-2 in large amounts in the blood and urine, as well as two unidentified iodinated substances, in three goitrous cretins. When T-1 and T-2 were given intravenously to euthyroids, the iodine which appeared in the urine was almost entirely inorganic iodide (I^-). When T-1 was given to these three goitrous patients, only limited deiodination occurred. When T-2 was injected, only T-2 appeared in the urine, and a thyroid slice from one patient would not deiodinate a diiodotyrosine substrate, whereas nodular goiter slices would deiodinate T-2. Also, close relatives of one patient, though normally developed, could not deiodinate T-2 as well as normals.

Stanbury and Querido[27] felt that the loss of hormone precursors (iodide, T-1 and T-2) resulted in hypothyroidism. This, in turn, called out excessive thyrotropin from the pituitary and resulted in thyroid hyperplasia. The recurrence in siblings would strongly suggest a genetic cause. They state that there are probably other types of metabolic cretinism which involve defects of synthesis, release, transport and utilization of hormone, which seems very likely to this writer.

Pathology

As in endemic goiter, various types of pathology are seen in these goiters, from simple colloid storage to widespread atrophy with fibrosis. Multiple changes are often seen in a single gland. The distinctive finding of areas of hyperplasia is evidence of overproduction and activity in the gland by thyrotropin (TSH). Hyperplasia should be present in all such glands, though some biopsies have not shown this. It may have been present in other areas. The hyperplasia is often intense and widespread, and may be seen in the adenomas.[26] Overproduction of TSH is due to the deficiency or absence of thyroid hormone production; the presence of thyroid tissue accounts for its reactive pattern[1, 8, 11, 14, 26] (Crane*). Included are thyroids which show simple colloid, hyperplasia, adenomas (involutional, embryonal and fetal), small acini with little colloid, areas of degeneration and atypism suggestive of malignancy (Table 5, L.G.)[14, 32]

It is more common to find more cases of diffuse goiter with hyperplasia in infancy; goiters with neoplastic and hyperplastic nodules in children six to 13 years; and diffuse, colloid and nodular goiters in adolescence.* This would suggest that pathology may change during the years of the affliction. Changes characteristic of malignancy are not common, even after some decades of duration. Metastases have not been reported.

Similar hyperplasia is induced by thiourea drugs,[14] sulfocyanides, soy

* J. T. Crane: Personal communication.

beans, rutabaga vegetables (cabbage, turnips, and the like) and cobaltous chloride. There is no substantiating evidence in the literature, however, nor in our cases, that such goitrogens have been the cause of any cases of human goitrous hypothyroidism. Cobaltous chloride, however, can induce hyperplastic goiter with depressed function, including I^{131} thyroid uptake.

CLINICAL FINDINGS

There are four siblings in the eight cases reported in this article (Table 5, AT and KT, AH and PH); of the six families, two definitely,

Fig. 4. P.H. Age (years); chronological, 4½; height, 3½; epiphysial, 3; mental, 3½. Onset of hypothyroidism, 3 to 6 months, and of goiter, 6 months. Her hypothyroidism was mild, though existent for 4 years. Some thyroxin probably was being formed.

and two others questionably, had multiple cases. It was estimated from other reports that as many as one half of siblings can be afflicted. These findings depend on the degree and duration of the untreated hypothyroidism, which usually precedes the appearance of goiter. Hypothyroidism will usually manifest itself within a few weeks after birth (the mother's hormone going through placenta may act as a replacement) and usually not later than three to six months. The author knows of several cases in which thyroid deficiency was so small that detection was not made until late childhood after goiter had appeared. Hypothyroidism may progress slowly or rapidly, although within several years it

usually becomes extreme; after five to 10 years it is almost total, resembling athyreosis.

The goiter may appear early, as in one of our cases (PH) at six months of age, or as late as 16 or more years. The goiter may be considered to be compensatory. It is possible that the unenlarged gland has areas of hyperplasia, especially if hypothyroidism is evident. High uptakes of I^{131}, as found in hyperthyroidism, are also found in such cases. Normal and subnormal uptakes are rare now.[16a]

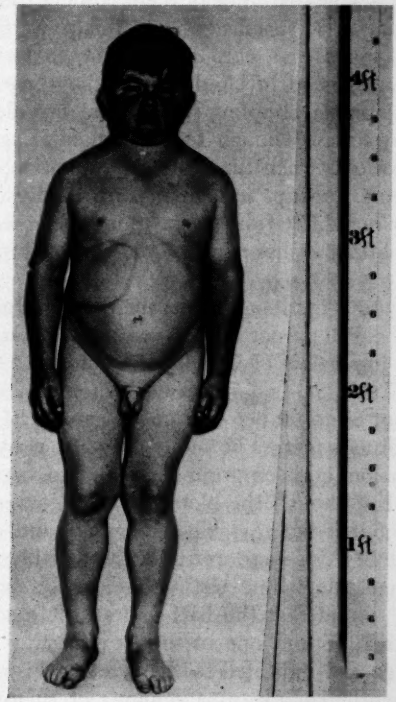

Fig. 5. A.D. Age (years): chronological, 19; height, 8½; epiphysial, 6; mental, 8. Onset of hypothyroidism, 6 months to one year, and possibly no goiter. This patient was never treated. He illustrates a deficiency of long duration and increasing amount.

One of our cases (BD), 8¾ years of age, showed definite hypothyroidism, but no goiter or extraneous thyroid could be detected by careful scintiscanning at the base of the tongue or thyroid, or retrosternally; her uptake of I^{131} was 90 per cent at 24 hours in a normal-sized thyroid. Her plasma also showed increased rate of formation and amount of organified iodine by the use of an anionic resin,[21] as with

hyperplasia. Another such case, AD, in which the goiter was not definitely detectable at 19½ years of age, had hyperplasia histologically.

Some findings merit discussion: one of these is the degree of myxedema. The longer the duration and the greater the degree of hypothyroidism, the more widespread and intense is the myxedema. Any myxedema is a demonstration of marked hypothyroidism. In our Clinic, untreated hypothyroidism of more than a few years' duration is exceptional. Most children do not have hypothyroidism for more than a few years before the start of therapy; myxedema then is not very intense or widespread. It is possible that some of them produce more thyroxin than others, but, of course, in insufficient amounts. Dwarfism may not be extreme; as with myxedema, this may be due to formation of some thyroxin. Their height-age in childhood is about equivalent to their epiphysial age. Epiphysial stippling (dysgenesis) may develop, as it does in untreated athyreotics. Though retarded, mental age is not too retarded in some patients when the degree and duration of deficiency are considered. Anemia, constipation, hernia, myocarditis and other common findings do not differ from those found in other types of hypothyroidism. Exophthalmos has not been recorded. A bruit is occasionally present.

Two laboratory tests merit comment: the PBI (protein-bound iodine) and I^{131} test. The PBI is not always very low; it can be in the low-normal range or just below (3.5 to 4 micrograms per 100 ml.—the low normal). BD (Table 5) had increased values, 11.2 and 10.3 micrograms. Only about 80 to 90 per cent of measured PBI in euthyroidism and hyperthyroidism is mature hormone. In goitrous hypothyroidism an increased conversion goes on from inorganic to organic iodine; the writer[21] thinks that, though the blood PBI is a low normal (or above normal), some of it is not thyroxin, but mono- and/or diiodotyrosine (Stanbury's type B[27]). A more exact measure of blood thyroxin is by the butanol-extractable iodine test (BEI), for it extracts little else. Pickering et al.[18] found that the BEI of four of these goitrous cretins (Table 5, AT, KT, JS and one of their cases) was definitely in the hypothyroid range and indicated to them, as to this writer, that these cretins do not synthesize adequate amounts of thyroxin. It is characteristic of the thyroid of a goitrous hypothyroid to take up much more I^{131} than that of a euthyroid, and is similar to that of the hyperplastic gland of hyperthyroidism. The I^{131} uptake starts soon, goes to a very high level, and often stays in the gland for less than the normal effective half-life* (three out of four of our cases), which is similar to hyper-

* Effective life is the time during which a substance exerts physiological effect. For radioisotopes, it is expressed as half-life, for, theoretically, radioisotopes decay physically for an almost infinite time. The usual effective half-life for I^{131} in a euthyroid is between six and eight days.

thyroidism. The amount converted[21] by some of our cases (five out of eight) to protein-bound material (organified, not mainly thyroxin) was increased as in hyperthyroidism.

Autoradiograms of blood on five patients (Table 5) showed: iodide, T-1 and/or T-2, T-4 in patients AH, PH, AT and BD;* iodide, ? T-1 and/or T-2, T-4 in patient KT. It was not possible to quantitate these fractions accurately; however, the lines had the following decreasing order of density: iodide, T-4, T-2 and/or T-1, and unknowns. AH, PH, AT and BD* resembled Stanbury's type C[27] lack of deiodination of iodotyrosines. Several autoradiograms had unidentified substances. In Stanbury's type A the administration of KSCN resulted in the rapid discharge of inorganic iodide from the gland. No organified iodine appears on the chromatograms of the blood, for none, or very little, is formed in the gland.

THERAPY

Thyroid extract, sodium L-thyroxin and L-triiodothyronine are available for replacement therapy. The first two are satisfactory; the last has not been used long enough to appraise properly. L-triiodothyronine is three or four times as potent as L-thyroxin, does not seem to raise the protein-bound iodine (organified) level as well as the first two, and induces toxicity more readily. Whether it will raise the intelligence quotient satisfactorily has not been reported; this would be a most important criterion, for no other benefit is more desired. Thyroid extract, given in adequate doses, has been found to be satisfactory. Equivalents are as follows: thyroid extract, 100 mg.; sodium L-thyroxin, 0.1 mg.; L-triiodothyronine, 25 to 35 micrograms. The doses should be started at low levels and gradually raised every seven to 14 days until full benefit is reached. The top daily dose for children probably is: thyroid extract, usually no more than 200 to 250 mg.; sodium L-thyroxin, 0.3 to 0.5 mg.; L-triiodothyronine, probably 25 to 50 micrograms. Toxicity, which should occur only rarely, can be controlled by reducing the dose or discontinuing it for some days (even as long as two weeks).

In the United States, surgery is indicated for the following reasons, and in this order: (1) for ruling our malignancy, for which biopsy of nodules or regional glands is often sufficient; (2) for compression or displacement of the trachea or, less commonly, the esophagus (this

* A chromatogram (BD) was done by the courtesy of Dr. S. C. Werner of Columbia University, New York City, who stated that only iodide was detected; and "there did appear in the serum thyroxine, triiodothyronine, diiodothyronine, monoiodotyrosine and unusually large amounts of iodide . . . at the origin . . . a peculiar iodoprotein which could conceivably even be thyroglobulin." Our radiochromatogram on BD is analyzed above in the text.

was required in two of our cases—PH and LG, Table 5); (3) for cosmetic reasons, when a large goiter and multiple nodulations are disfiguring.

Subtotal thyroidectomy is done for the latter two indications. Shrinkage by thyroid medication could be tried, and, when the gland size is constant, thyroidectomy could be done.

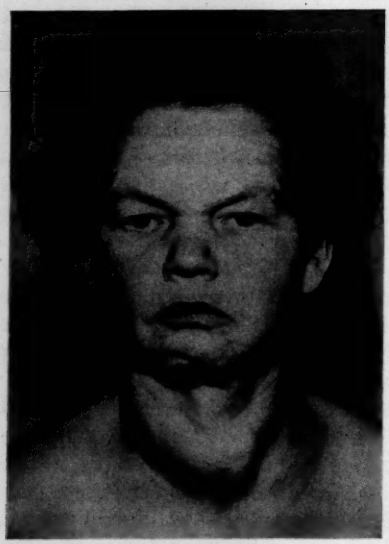

Fig. 6. L.G. Age (years): chronological, 44; height, 10; epiphysial, 18; mentality very retarded. Onset of hypothyroidism at one to 2 years, and of goiter at 3 years. Thyroidectomy performed at 8, 14, 43 and 44 years. Growth ceased at about 18 years, when epiphysial age may have been below 10 years. All epiphyses closed when the patient was first examined for this at 44 years. Thyroid first prescribed at age 14 years in probably insufficient dosage and continued to age 27. From 27 to 38 years, ¾ grain daily; from 38 to 44 years, ½ grain. Over all these years the dosage was inadequate, as evidenced now by recurrence of goiter, dwarfism, myxedema, anemia, amenorrhea, constipation, thin hair, and other manifestations. "Too little and too late!" (Courtesy of M. J. Nyda, M.D., San Francisco.)

Families who have goitrous hypothyroid children should be appraised of the fact that there may be recurrence in nearly half of their offspring.

PROGNOSIS

Therapy started in childhood is usually successful. The benefits vary with the previous degree and duration of the deficiency. The goiter may diminish, or even disappear in a short time (as in AH, Table 5). Physical growth may accelerate toward normal; mental age may progress

to a higher level, although, occasionally, it may only plateau (it has seldom been noted to diminish). Several of our patients (Table 5) acquired fairly good mentality. A good example is that of PH, hypothyroid since the age of six months, who was not treated until the age of 4½ years, at which time her IQ was 75. At nine years it had reached 101, and she went on to complete her college education successfully. It is possible that before hypothyroidism she had a potentially superior intelligence which was not attained because of the duration of deficiency during the vital years—six months to 4½ years—before therapy was started.

The appearance of facies, activity of the child, anemia, constipation, myxedema, yellow coloration of skin, and so forth, each change for the better—sometimes with surprising rapidity when the previous degree of deficiency is considered. The majority of these patients do not live out the usual life span because of cardiac and coronary insufficiency or acquired infection.

There are reports of spontaneous overactivity of the goitrous hypothyroid gland (not due to thyroid medication) which results in euthyroidism or even hyperthyroidism, as in three cases reported by Hurxthal and Musulin[11] and two others reported by Bartels.[14] Hurxthal and Musulin reported that ". . . cretins with goiter may develop normal thyroid activity," and Bartels states ". . . adenomatous goiters in cretins may cause a spontaneous return of thyroid function in some . . ." It is the opinion of the author that such spontaneous generation of normal thyroid hormone must be rare; however, a toxic adenoma could generate extra thyroxin and result in these developments. We may have encountered a somewhat similar case which is not reported in Table 5 (No. 239884), who may have been hypothyroid without goiter from the age of 4¾ to 5¾ years, when a nodular goiter developed. She was then clinically euthyroid, but had 62 per cent uptake of I^{131}. The tissue was hyperplastic, and she was operated on at the age of seven years.

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INFANTILE HYPOTHYROIDISM

Diagnosis and Treatment

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Among the ubiquitous metabolic and growth effects of thyroid privation in early infancy, those relating to the central nervous system, its development and its function, are of primary concern. In addition to mental retardation, many and varied behavioral and neurological aberrations relating to central nervous system pathology are common in children deficient of thyroid through the early months of life.[20, 22, 32, 36] These may include emotional lability, speech impediments, obsessive behavior, defects in abstract reasoning, neurological abnormalities such as spasticity, hyperactive reflexes and tremors, and electroencephalographic changes. The anatomico-pathologic effects of hypothyroidism on the developing brain, in addition to inadequate growth, include vascular changes, retarded or deficient myelinization, delayed appearance of fiber tracts, delayed neurological maturation, and neuronal degeneration. In long-standing deficiency there is a decreased number of cortical cells.[9, 10, 13, 18, 25] There is little likelihood that these effects, once established, are subject to reversal.

Normally, growth and development of the central nervous system is most marked during the initial months of life; thereafter it decreases rapidly (Fig. 7). Postnatal growth and development of the brain, represented by increment in weight, is half completed by six months of age and two thirds accomplished by the age of one year.[40] It is during this period of most rapid growth and development that thyroid deprivation exerts its severest central nervous system effects.

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Permanent neurological and intellectual impairment is generally most severe in endemic cretins and in sporadic cretins with deficiency manifest at birth (retarded bone age and physical signs of hypothyroidism);[5, 36] in each instance an intrauterine hormone deficiency no doubt exists, being secondary to maternal deficiency in the former and placental dysfunction in the latter. In infants with only partial thyroid deficiency the incidence of severe mental retardation is less than in the completely athyroid infant similarly treated.[36] Acquired hypothyroidism beginning after infancy is rarely associated with mental deficiency or neurological residua if such cases are adequately treated within a reason-

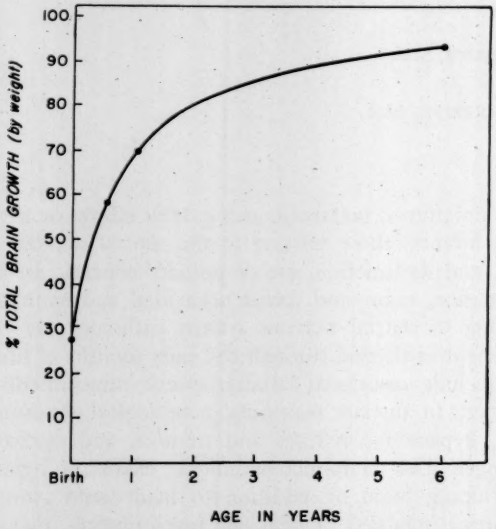


Fig. 7. Postnatal brain growth. (Modified from the White House Conference on Child Health and Protection—Growth and Development of the Child, part II, Anatomy and Physiology. New York, Century Company, 1933.)

able time.[1, 12, 36] The severity of permanent central nervous system effects of thyroid deficiency seems to parallel the relative immaturity of the central nervous system at the onset of deficiency, the degree of deficiency, and its duration before correction; i.e., effects are progressively less severe with increasing age at onset and shorter periods of time between diagnosis and the institution of adequate therapy.[1, 12, 36] The child's hereditary intellectual endowment is also of importance.

It has been observed in our laboratory that in the athyroid monkey those tissues more directly concerned with energy metabolism (gastrointestinal system, skin and muscle, cardiovascular and renal tissues)

require lower levels of circulating thyroxin for normal function than do the skeletal and central nervous systems.[26, 26a, 30]

A similar discrepancy in tissue response has also been observed in hypothyroid children under treatment. When the therapeutic response is judged only by superficial signs and symptoms relating to liver function, energy metabolism, and cardiovascular and renal function, such children may appear normal, but be inadequately treated. The adequacy of treatment in the rapidly growing infant or child should be evaluated relative to optimal growth and development of the skeletal and central nervous systems, and serum hormonal iodine serially determined to ensure that the plasma level of hormone is kept well within normal limits.

CLINICAL CLASSIFICATION AND COMMENTS

There are at least two distinct types of sporadic cretinism in the United States: congenital thyroid agenesis (or hypogenesis), which accounts for approximately 90 per cent of sporadic cretins, and familial goitrous hypothyroidism, which accounts for approximately 10 per cent of sporadic cretins.[17, 21, 31, 37]

Sporadic thyroid agenesis is usually complete and symptoms appear shortly after birth. Some residual functioning tissue occasionally exists and allows for milder symptoms with resulting delay in their recognition.

Familial goitrous hypothyroidism is a genetically determined defect in thyroxin synthesis (possibly a deficiency in oxidative enzymes responsible for conversion of iodide to hypoiodite and final precursor linkage)[31] transmitted as a recessive autosomal gene. Both sexes are equally involved, and up to 50 per cent of offspring in any one family may be involved. This condition may not appear until later in childhood. Goiter is usually absent at birth, and I^{131} uptake studies are frequently necessary for differentiation between the two varieties of sporadic cretinism.

The majority of the athyroid infants appear normal at birth. As existing hormone (transplacentally acquired) undergoes degradation, signs of deficiency gradually appear. This process requires three to four weeks.* The early symptoms are nonspecific and include poor feeding, wrinkled brow, constipation, lethargy, and undue coldness and mottling of the extremities.

The respiratory system is frequently involved early with accumulation of "myxedema" in retropharyngeal, hypopharyngeal and nasal tissues and interference with normal respiratory exchange. Respiratory symptoms may resemble those of nonspecific recurrent or chronic infections. Several hypothyroid children in our Clinic have been worked up or treated for congenital pulmonary or cardiac disease.

* Placental dysfunction may be the basis for the occasional sporadic cretin manifesting hypothyroidism at birth

Carotenosis (and carotenemia) may be present and overlooked as "physiologic jaundice." Persistence of "jaundice" with the foregoing nonspecific symptoms should arouse suspicion.

Classical signs and symptoms of cretinism, in addition to those mentioned, are listed according to organ system involved.

NERVOUS SYSTEM
- Hyporeflexia
- Persisting infantile reflexes
- Mental retardation
- Neurologic evidence of organic damage

SKELETAL
- Characteristic facies—depressed nasal bridge, open fontanels, relatively narrow forehead (myxedematous cheeks), mandibular hypoplasia
- Retarded dental development
- Depressed long bone growth
- X-ray
  - Depressed bony maturation
  - Changes in calcification patterns
    - Epiphysial dysgenesis
    - Poor cortical bony differentiation
    - Increased bone density

CARDIOVASCULAR-RENAL
- Hypotension
- Bradycardia
- Depressed circulation time
- Depressed renal function

GASTROINTESTINAL AND LIVER
- Depressed liver function
- Elevated cholesterol
- Carotenemia
- Flat glucose tolerance curve
- Constipation

SKIN AND MUSCLE
- Depressed BMR and hypothermia
- Decreased creatine excretion
- Hypotonia
- Lethargy
- Thickened dry skin
- Hair and nail changes
- Myxedema accumulations

By the time that classic symptomatology is evident, some degree of central nervous system damage may already have occurred.

X-RAY AND LABORATORY EVALUATION

In infants the suspected diagnosis is best confirmed by x-ray examination, by determination of the serum hormonal iodine concentration and, in certain instances, by determination of I^{131} uptake by the thyroid gland.

Initial radiographic evaluation should include films of hands and

wrists, shoulders, feet, knees and hips. Changes to be looked for include the delayed appearance and immature configuration of secondary centers of ossification, epiphysial dysgenesis and delayed linear growth of long bones.[3, 23, 32a, 41, 42] Less significant features include increased bone density and cortical thickening. Reference standards for evaluation of skeletal age include those of Stuart for the feet (as reproduced by Caffey[2a]), Gruelich and Pyle for the hand and wrist,[15] and Pyle and Hoerr for the knee.[31a]

The presence of intrauterine thyroid deficiency may be suspected in the absence of ossification centers for the distal femur and/or the proximal tibia. Reference to the standards for appearance of intrauterine ossification centers in Caffey's book[2a] will allow confirmation and estimation of duration of intrauterine deficiency.[29]

The relatively rapid appearance of secondary ossification centers in the foot during the first year allows utilization of serial films of this area along with serial films of the hand and wrist as satisfactory follow-up evaluation of therapy. We have found serial hand and wrist films quite satisfactory for follow-up evaluation between one and six years of age. After this age, when changes in the hand and wrist are less rapid, the added evaluation of serial knee films is helpful.

The serum hormonal iodine concentration may be determined by one of two methods: BEI (butanol-extractable iodine) or PBI (protein-bound iodine or serum-precipitable iodine [SPI]). The BEI determination principally measures thyroxin and triiodothyronine; whereas, in addition, PBI measures mono- and di-iodotyrosine and iodinated proteins. Administration of inorganic iodide preparations (hydriodic acid, potassium iodide, and the like) does not interfere with BEI determinations, whereas it does with PBI determinations.

The relatively greater accuracy of the BEI method as compared to the PBI method, particularly in the lower than normal range, makes that procedure of definite choice in the substantiation of suspect hypothyroidism in the borderline case.[19] The following table of values (compiled from this and other laboratories) represents acceptable lower limits of normal for serum hormonal iodine concentration (BEI and PBI) in children.[7, 8, 19, 24, 29]

TABLE 6. *Serum Hormonal Iodine in Children; Lower Limits of Normal*

METHOD	AGE	VALUE (μgm. %)
BEI.....	<1 month	5.0
	1–12 months	4.5
	1 year–puberty	4.0
PBI.....	<1 month	6
	1–12 months	5
	1 year–puberty	4.5

The determination of I^{131} uptake by thyroid will assist in differentiating the athyroid sporadic cretin from the familial goitrous hypothyroid child with or without goiter.[31, 35] In the goitrous or potentially goitrous sporadic (familial) cretin, I^{131} uptake by thyroid is usually greater than normal; whereas nongoitrous sporadic cretins always have low or absent uptake. The uptake of I^{131} by thyroid may also be of value in differentiation of primary and secondary hypothyroidism. In pituitary hypothyroidism I^{131} uptake is low and may resemble primary hypothyroidism; however, it usually undergoes a significant increase after administration of pituitary thyroid-stimulating hormone.[28] With detection equipment now available I^{131} uptake studies may be satisfactorily conducted with 0.1 to 0.5 microcurie of the isotope.

The determination of serum cholesterol is unreliable as a diagnostic aid during infancy.[12] Serum carotene concentration may be elevated during infancy.[1, 12] Serum alkaline phosphatase concentration is depressed in hypothyroid infants and children.[38a] The determination of basal metabolic rate in infants and children is impractical.

TREATMENT

Na-l-Thyroxin* and Thyroid USP are equally satisfactory agents in the treatment of hypothyroidism in infancy and childhood. We have avoided the clinical use of l-triiodothyronine because the ability of that compound to produce normal skeletal and central nervous system growth and development in the thyroid-deficient infant has not been established. Na-l-Thyroxin has been used successfully by the authors in treating many hypothyroid infants and children during the past several years. Serum hormonal iodine values tend to be constant with any given dosage, and optimal therapeutic results are easily achieved without untoward toxic manifestations.

The immediate introduction of fully adequate doses of Na-l-Thyroxin to the athyroid infant is desirable and is not accompanied by adverse side effects. To endanger mental development for several months while gradually increasing from homeopathic to the desired dosage levels is irrational.

The average dose of Na-l-Thyroxin or Thyroxin USP required to bring about therapeutic response in the hypothyroid infant or child is presented in Figure 8. The doses shown, determined in our laboratories and clinics, correlate well with other estimates of daily hormone production.[6, 12, 34, 38] It will be noted that 0.1 mg. of Na-l-Thyroxin is considered the approximate equivalent of 90 mg. of Thyroid USP.[6, 33, 34, 38, 43]

* Na-l-Thyroxin may be obtained as Synthroid from Tranenol Laboratories, Morton Grove, Ill., or as L-Thyroxine Sodium from Haack Laboratories, Portland, Oregon.

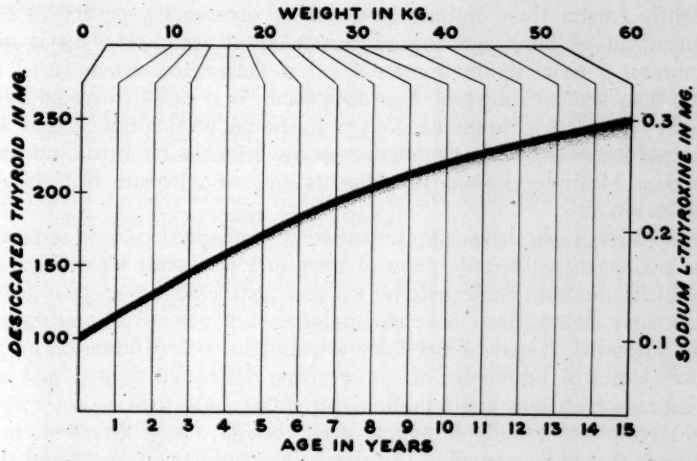


Fig. 8. Thyroid therapy in hypothyroidism of infancy and childhood. (Reprinted with permission of A.M.A. *Am. J. Dis. Child.*[12])

FOLLOW-UP STUDIES

A continuous re-evaluation of infants and children under treatment is essential to good management. A careful history for evidence of persisting signs of deficiency and carefully recorded physical measurements are important. Serial determinations of serum hormonal iodine and serial x-ray studies offer valuable objective criteria as to the adequacy of treatment. Initial and follow-up psychometric examinations are also desirable. We follow up our patients at monthly intervals during the first six to nine months, and at three to four month intervals throughout the remainder of infancy.

Hormonal iodine levels are determined as frequently as is necessary to insure that optimal serum levels are maintained. Values in children under treatment with desiccated thyroid should range between 5 and 8 micrograms per 100 ml., and with Na-l-Thyroxin, between 6 and 10 micrograms.

The serial roentgenographic evaluation of skeletal maturation provides a valuable objective estimation of the adequacy of treatment. Repeat x-ray studies are conducted at three month intervals during the first year; at six month intervals for the next two to three years, and less frequently thereafter. Acceleration of skeletal maturation should be obvious before three months of therapy, and bone age deficits should soon be corrected. Epiphysial dysgenesis disappears with adequate therapy. Long bone growth, while visible by x-ray, is more readily appraised by physical measurements of the patient. If hormone dosage is maintained at

slightly greater than optimal levels, there occasionally occurs an advancement of bone age beyond chronological age.[4, 5, 12] This is uncommon if serial serum hormonal iodine determinations are used in case management; however, if it does occur, it is easily corrected by a slight reduction in hormone dosage. It should be mentioned that accelerated growth and development requires optimal vitamin and mineral intakes. Multiple vitamin supplements and an adequate diet should be maintained.

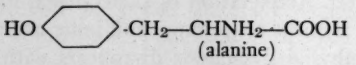
In children who have been untreated for prolonged periods and who are permanently mentally retarded there may occur untoward behavior problems on doses inadequate for optimal replacement. Such manifestations may include destructiveness, negativism, hyperactivity, restlessness and insomnia. It may be necessary to maintain such children on inadequate doses of hormone. Infants receiving desiccated thyroid may exhibit transient signs and symptoms suggesting mild toxicity; such signs and symptoms usually disappear even though dosage is maintained. Parents should be warned of this possibility. We have not observed this reaction with Na-l-Thyroxin.

SUMMARY

It is to be re-emphasized that in the cretin infant the earliest possible institution of optimal hormone therapy offers the only hope for final realization of his innate intellectual endowment. Hormone dosage must be maintained at levels compatible with normal brain and bone growth and development, even at the risk of an occasional transient toxicity.

EDITOR'S NOTE. It is thought now that the thyroid produces a family of hormones. These consist of thyroxin (t_4), triiodothyronine (t_3), the thyroxin tetraiodothyroacetic acid (TETRAC or t_4 ac) and triiodothyroacetic acid (TRIAC or t_3 ac); the latter two have been postulated as likely metabolites of thyroxin and triiodothyronine. There are two other possible hormones: mono- and/or di-iodotyrosine (t_1 and t_2). The "mother" substance, t_4, may well include the actions of the others. There is good evidence that t_3 is formed from t_4 in the peripheral tissues and that t_3 is the active form of t_4. TRIAC may be useful in reducing the amount of cholesterol present in coronary artery disease. TETRAC has given beneficial results in myxedema. T_3, t_4 and t_3 ac have been shown to have about the same effects on blood cholesterol and basal metabolic rate. Nothing is known to date on the effects of triiodothyronines on skeletal or mental growth of children. Knowledge on the latter point is greatly needed, for this would be a most important criterion in the treatment of childhood hypothyroidism. T_1 and t_2 have no known beneficial effects.

These various hormones are chemical variants of thyronines. A thyronine is formed from two tyrosine molecules. A tyrosine molecule fundamentally is a benzene ring plus an alanine side chain and a hydroxyl group in the para position:



When thyronine is formed, there is a loss of an alanine from one and a hydrogen from the other molecule. Iodination of the tyrosines can be done at several different positions on the two rings. W.A.R.

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ISOSEXUAL PRECOCITY IN BOYS AND GIRLS

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When precocious sexual development is of the sex appropriate to the patient's own sex, it is called *isosexual* precocity. A variety of factors may be involved in the causation of precocity. Precocity may be evidenced by the reproduction of all the changes that normally take place at adolescence, such as are seen in so-called constitutional or idiopathic precocity. The occurrence of some of these cases in familial distributions has suggested a hereditary factor.[10a] On the other hand, precocity may express itself as the isolated effect of androgen or estrogen, without all the concomitant developmental changes of normal adolescence. The latter type is exemplified in macrogenitosomia praecox in boys due to congenital adrenal hyperplasia, or, in girls, the presence of an estrogen-producing neoplasm. The following discussion will take up isosexual precocity first in boys, and secondly in girls.

ISOSEXUAL PRECOCITY IN BOYS

IDIOPATHIC OR CONSTITUTIONAL PRECOCITY

Probably the most common form of isosexual precocity in the male is that type in which the causative factor cannot be identified. These children show a precocious, complete or nearly complete adolescence without evidence of cerebral or other organic abnormality, suggesting that unknown factors have caused activation of the pituitary gonadotropic hormones at an earlier time than in the normal child. The diagnosis is one of exclusion.

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CASE HISTORY. A white, male infant had an uneventful birth and neonatal course. At age 6 months his parents noted that his penis appeared to be larger than normal. Several months later pubic hair appeared. His physical features gradually assumed an adult, masculine look, especially his face. He became very strong with well developed muscles and with deepening of his voice. By the age of 2½ years his voice closely resembled that of an adult man. Both his penis and testes were greatly enlarged. There was pubic hair without axillary hair at this age. No neurological abnormalities could be found. Urinary excretion of 17-ketosteroids was slightly above the normal limits for his age. Pneumoencephalographic studies revealed no evidence of intracranial disease. The parents were advised of the nature of the child's precocity, and supportive counselling was offered to them to enable them to understand what was in store for them and the child.

DIAGNOSIS. As in the case history presented above, boys with constitutional precocity have testes enlarged proportionately to the enlargement of their penis. This is in contradistinction to what is found in boys with congenital adrenal hyperplasia or virilizing adrenal tumor, when the testes are relatively smaller. Furthermore, there is no remarkable elevation over adult values of the urinary 17-ketosteroids in boys with constitutional precocity, whereas in congenital adrenal hyperplasia and virilizing adrenal tumor there may be exceedingly high values for these steroids in the urine. Gonadotropin excretion values similar to those of the adult are seen in boys with constitutional precocity. These hormones are not usually measurable in the urine of boys with congenital adrenal hyperplasia or virilizing adrenal tumor.

The general physical examination of the boys with constitutional precocity shows development of all the aspects of adolescence at a very early age. There is enlargement of both testes and penis, pubic and axillary hair usually appearing in the same order seen in the normal adolescent.

TREATMENT. Although in the past children with constitutional precocity were submitted to extensive therapy with x-ray of their pituitary or pineal gland, there appears to be no justification for such drastic treatment. The most important therapeutic contribution the physician can make is to advise with the parents in the psychological handling of the child. Money and Hampson have recently enunciated a series of important guides to case management which have come out of their extensive studies of this condition.[13] The following guides have been condensed from their work:

1. Children with sexual precocity have excessive physical energy and strength, and their plethora of such activity is the main problem their parents must face. This appears to be more true with the boys than the girls. Parents must be prepared to provide increasing avenues for activity as the infant grows larger. Cramped residential quarters in an urban setting have not proved very satisfactory for these children.

2. These children appear to react most favorably if they are told exactly and specifically what is wrong with them. Money and Hampson

found that providing them with a factual, medical account of their abnormality gave them something concrete to think about, and served to prevent their developing elaborate fantasies concerning their condition. These authors feel that this information can be provided by a competent medical advisor who is held in respect by the child, and that special psychiatric services need be asked for only if there is obvious disturbance.

3. From an early age children with precocity need specific facts concerning sex education so to avoid their picking up distorted information by the usual unofficial channels. This would seem to be somewhat more important with these children than with normal children.

4. Money and Hampson[13] found that sexually precocious children were as capable of regulating their sexual conduct as were normal *adolescents*, this being done well or badly according to the adequacy of their environment. They believe that greatest success can be anticipated in the handling of these children if they are informed in a straightforward manner of what is expected of them regarding social and moral standards. It is particularly important to explain to them why such social and moral standards have to exist.

5. Masturbation may or may not be found as a habit in children with precocity. The male children tend to have frequent and spontaneous erections. The above-mentioned authors suggest that masturbation not be forbidden, but that the child be told that it is the sort of thing that will offend people if carried out in public.

6. Precocity in social spheres may or may not be present in these children. There is a tendency for precocious children to seek out as playmates children of similar physical build (i.e., older children). This may in fact be beneficial to them, since they are thereby not constantly reminded of the disproportion between themselves and their playmates. The precocious child may need special coaching in order to develop the skills necessary for successful play with his somatic equals, since he has not had as many years of practice as they have. It has been found that progress in schoolwork may safely be accelerated if the intellectual performance of the child in tests is not inconsistent with such progress.

7. There is no evidence that sexually precocious children are any more liable to psychological maladjustment than normal children, environmental influences being equally adequate.

8. The physical appearance and superficial behavior of these children usually tempt one to treat them according to their apparent age. Of course the child cannot measure up to such standards of expected performance, and for this reason all persons who work with these children should constantly remind themselves of this discrepancy.

Boys with constitutional precocity occur only rarely. In the series described by Jolly[10] there were only three boys with constitutional

precocity out of a series of 19 precocious boys. It has been this author's experience, as it has of others, that the handling of boys with constitutional precocity does not present the complexities presented by girls with this syndrome.

PRECOCITY DUE TO ADRENAL DISEASE

Overproduction of androgens by the adrenal cortex in boys gives rise to precocity of a special type. As mentioned, the size of the testes in these boys is small relative to the size of the penis. This variety of precocity may be caused by congenital adrenal hyperplasia, virilizing adrenal tumor or Cushing's syndrome.

Congenital Adrenal Hyperplasia

The term "macrogenitosomia praecox" has long been attached to this condition in boys. It is caused by a metabolic error which is apparently inherited as a mendelian recessive. This metabolic error consists in an inability to biosynthesize adequate amounts of hydrocortisone by the adrenal, and leads to an overproduction of 17-ketosteroid precursors. It is the latter aspect of the abnormality that results in the masculine type of precocity.

There is a progressive enlargement of the penis, which in some male infants with the condition is noted shortly after birth, and in others (the majority) may not be detected for one to four years. There is early deepening of the voice, acne, and the development of pubic and axillary hair.

CASE HISTORY. At age 1½ years it had been noted by the parents that this child's penis was larger than normal. When the boy went to kindergarten at age 5 years, the school physician found a growth of pubic hair and a definitely enlarged penis. It was then, in retrospect, that the parents realized that the child had grown more rapidly and that his musculature was more marked than would ordinarily be expected for his age. This is not an uncommon order of events when the affected child is the first boy, as in this family. By age 7 years the boy showed the appearance demonstrated in Figure 9. His blood pressure was normal. His urinary 17-ketosteroid excretion was approximately 30 mg. per 24 hours. His precocious development of height, weight and osseous maturation are depicted in Figure 10. His testes were small in comparison to his penis. Although cortisone therapy reduced the urinary 17-ketosteroid excretion to normal, the accelerated osseous maturation continued. It appears that as a result of this the boy reached his maximal height before the age of 10 years. It is believed that the cortisone treatment came too late to decelerate his epiphysial closure.

COMMENT. Some infants with this syndrome of congenital adrenal hyperplasia show excessive urinary sodium loss as a component part of the syndrome. This is a serious complication, and the interested reader is referred elsewhere for its diagnosis and treatment.[5] Often there is

abnormally great skin pigmentation in these patients. Other variations on this metabolic theme have been reported.[6]

DIAGNOSIS. The finding of elevated urinary 17-ketosteroids in such a boy is probably the single most helpful diagnostic procedure. Observation of relatively small testes with a large penis is helpful, but unfortunately a few of the males with congenital adrenal hyperplasia have large testes as a result of the proliferation of adrenal rest tissue in the

Fig. 9. Boy with congenital adrenal hyperplasia (age 7 years). Note that scrotum is obscured by adult-size penis.

testis. Thus this diagnostic point is made less certain. Of course it is important to differentiate congenital adrenal hyperplasia from virilizing adrenal tumor, since treatment of the former is medical and treatment of the latter is surgical. At present the most useful diagnostic procedures are (1) therapeutic test with cortisone, which causes suppression of urinary 17-ketosteroids in congenital adrenal hyperplasia, but not in cases of virilizing tumor or in Cushing's syndrome; (2) estimation of increased urinary excretion of dehydroepiandrosterone. This steroid is excreted in large amounts by most patients with virilizing adrenal

tumor and is usually estimated by Allen's colorimetric method.[7] (3) Estimation of urinary pregnanediol excretion. Patients with congenital adrenal hyperplasia excrete increased amounts of this steroid.[2]

TREATMENT. The most immediate problem to be dealt with in boys with congenital adrenal hyperplasia is the psychological reaction to the precocity. The guides to the management of this have been outlined in the previous section. As soon as the boy goes to kindergarten the

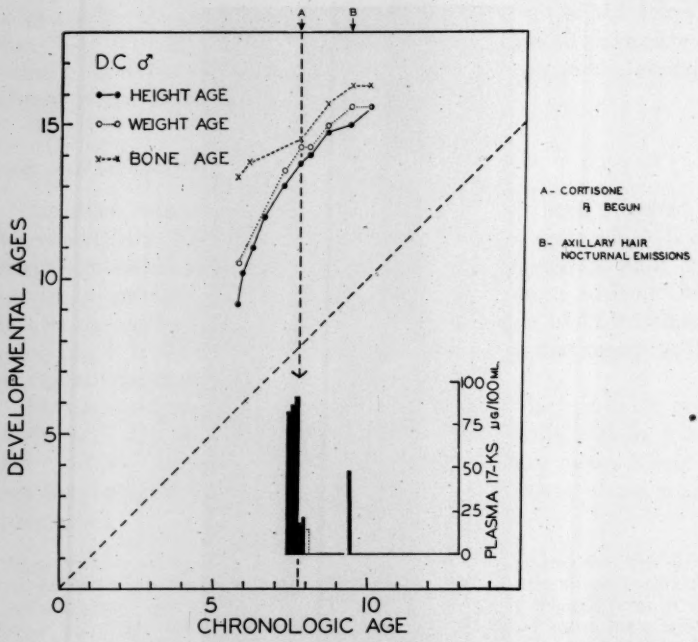

Fig. 10. Developmental chart of patient shown in Figure 9. Note marked acceleration of growth and osseous maturation.

problem of adaptation becomes acute. In the experience of this author there has been no evidence that the libido of these children with congenital adrenal hyperplasia is any different from that of other children their age. This is an observation which may have to be pointed out to school officials. Furthermore, because of the rapid growth of these boys, such a child may not fit the desk available to him in school, and an effort should be made to make him comfortable at a suitable desk. The intellectual performance of these children, as is also true in constitutional precocity, is no different from the normal.

Cortisone or hydrocortisone therapy will suppress the excessive production of androgen in these boys, as has now been repeatedly veri-

fied.[14] There is not general agreement, however, on the advisability of such medical therapy in boys with the precocity of congenital adrenal hyperplasia. If the bone age of the patient is less than 11 years,[19] there appears to be a good chance that the precocity and excessive growth will be arrested. Under these conditions medical therapy offers a real advantage. For the child whose bone age is over 11 years, however, experience has shown that these boys go into precocious adolescence when cortisone or hydrocortisone therapy suppresses the excessive production of androgen and thus releases the normal pituitary-gonadal mechanism of puberty. Since such a boy's chronological age may be only six to eight years, this rather complicates the management of the case, for the child now develops precocious adolescence, including nocturnal emissions and fertility (cf. Fig. 10).

Virilizing Adrenal Tumor

The male child with virilizing adrenal tumor may show no superficial clinical differences from the child with congenital adrenal hyperplasia (see Fig. 9). There have been no reports of excess pigmentation in these children, such as occurs often in congenital adrenal hyperplasia. This physical finding, however, is of little diagnostic value because of the broad spectrum of skin pigmentation in our population.

CASE HISTORY. A white, male child had an enlarged penis at the age of 3 years, followed in a few months by pubic hair. There was one normal older male sibling. At the age of 3 5/12 years he was found to have a height age of 4 years and a bone age between 4 and 6 years. Pyelograms showed the presence of a mass on the left side of the abdomen, depressing the left kidney. Assay for urinary gonadotropins was negative. Operation was refused. By age 4 3/4 years his height age was 8 years and his bone age 12 years. The penis was large, but the testes showed no particular enlargement for his chronological age. Urinary 17-ketosteroid values ranged between 150 and 50 mg. a day, as shown in Figure 11. This figure also demonstrated graphically the lack of suppression of 17-ketosteroid excretion when cortisone was given. The Allen reaction* for dehydroepiandrosterone was strongly positive in the urine specimens from this patient

* The Allen reaction is performed as follows: The patient's urine is acid-hydrolyzed, extracted, washed with base and evaporated to a residue by whatever method the hospital laboratory uses for the routine determination of 17-ketosteroids. The Allen reaction is run on the urine residue prepared just as for the Zimmermann reaction for 17-ketosteroids. An aliquot of residue is used which represents 25 to 50 ml. of urine. Three milliliters of an ethanol-sulfuric acid solution (1 volume of 95 per cent ethanol: 4 volumes of concentrated sulfuric acid) is added to the residue in a small Erlenmeyer flask. The flask is kept in a warm water bath (such as comes out of the hot water tap) at about 55° C. for 12 minutes. The flask is cooled for 1 minute in cold running water, and then 4 ml. of 95 per cent ethanol are added with swirling. The flask is cooled again in cold running water. The colors develop immediately. Almost without exception the cases of virilizing adrenal tumor thus far tested have shown an intense blue color with this reaction. The normal person's urine residue produces a brownish color. If the patient with virilizing adrenal tumor is excreting a great deal of dehydroepiandrosterone, the Allen test may closely resemble blue ink, and the deep blue color may not be appreciated until a strong light is held behind the flask.

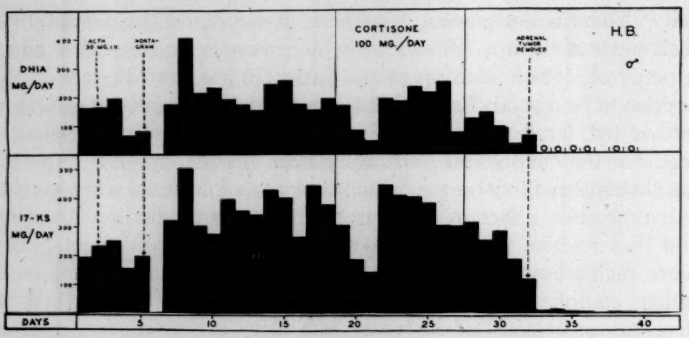

Fig. 11. Studies on a boy with virilizing adrenal tumor. Administration of cortisone failed to suppress the urinary excretion of 17-ketosteroids.

(see Fig. 12). After operation there was a striking reduction of the urinary 17-ketosteroids to values for a normal child his age (cf. Fig. 11).

COMMENT. The diagnosis of adrenal tumor in this patient was facilitated by the excessive amounts of steroids being excreted, especially those of the dehydroepiandrosterone fraction. *Patients have been described with virilizing adrenal tumors who excreted scarcely elevated amounts of urinary steroids;* for this reason a negative finding should never suffice to exclude an adrenal tumor.

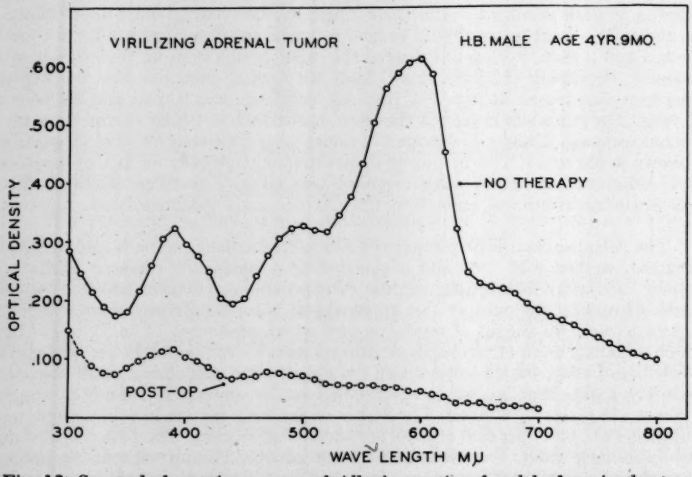

Fig. 12. Spectral absorption curves of Allen's reaction for dehydroepiandrosterone on the urine residue of a boy with virilizing adrenal tumor. Before operation the reaction was as blue as ink (note spectral peak at 600 millimicrons). Postoperatively the reaction was light tan as in normal persons. See footnote on p. 879 for details of the procedure.

Adrenal Tumor Causing Precocity and Cushing's Syndrome

This combination is an extremely rare cause of precocity in children. Wilkins and Ravitch have described a 2 11/12-year-old child with signs of virilism and Cushing's syndrome who was found to have an adrenal tumor imbedded in the substance of the right lobe of the liver.[17] Sobel et al. have described two boys with precocity and some evidence of Cushing's syndrome who were found to have adrenocortical tumors.[16] As yet there is no successful medical treatment for this condition, so that prompt surgery is indicated.

PRECOCITY DUE TO TESTICULAR DISEASE

Interstitial Cell Tumor

As of 1955 there had been described 14 cases of interstitial cell tumor of the testis producing sexual precocity.[3, 9, 10] Nearly all these cases had been seen in boys from the second to the sixth year of life. Six of the patients were either five or six years old. Why there should be this peculiarly specific predisposition for a rather narrow age range is entirely unknown. In all these cases described, a unilateral testicular tumor mass was found. Otherwise, the external physical examination and history were no different from what is found in constitutional precocity.

It is important to differentiate this condition from congenital adrenal hyperplasia in the male, since the latter condition may also exhibit nests of adrenal "rest" cells in the testes with palpable testicular masses. If the urinary 17-ketosteroids fall to normal values when cortisone is given, then the condition is almost certainly congenital adrenal hyperplasia. In this situation orchiectomy is not necessary, since the medical treatment of congenital adrenal hyperplasia with cortisone or hydrocortisone will cause regression of hyperplastic adrenal rest tissue in any location. If the urinary 17-ketosteroids cannot be suppressed with cortisone, then the diagnosis probably *is* interstitial cell tumor, and surgical treatment is indicated. If the urinary 17-ketosteroids still remain elevated after orchiectomy, then a careful search should be made for other tumor masses. Since Cook et al. showed that the urinary 17-ketosteroids from their patient were predominantly of the 3-alpha-OH-type,[3] it is not likely that the Allen test for dehydroepiandrosterone would be of value in the diagnosis of this condition.

PRECOCITY DUE TO CEREBRAL DISEASE

Precocity associated with lesions of the hypothalamus appears to occur more frequently in boys than in girls.[1, 10, 18] There are a number

of different abnormalities of the general area of the posterior hypothalamus which have been associated with precocity. Precocity may occur in connection with posterior hypothalamic tumors, encephalitis, tuberous sclerosis, craniopharyngiomas, and neoplasms of the pineal gland. The prognosis in most of these conditions is not good, especially in the case of the tumors, because of their location.

The McCune-Albright syndrome of sexual precocity, skin pigmentation and polyostotic fibrous dysplasia occurs rarely in boys, only four cases having been reported when Jolly reviewed the literature in 1955.[10] It is not certain that this syndrome is of cerebral origin, although there have been suggestive findings at autopsy. There is no specific treatment known, other than the guides to management of precocity in general already discussed.

ISOSEXUAL PRECOCITY IN GIRLS

Precocious puberty in girls along female lines presents a somewhat more complicated problem to the physician than does the male counterpart just discussed. Lloyd has recently published a teaching clinic which reviews several case examples of this condition.[12]

IDIOPATHIC OR CONSTITUTIONAL PRECOCITY

The incidence of constitutional precocity in girls is much higher than in boys. In Jolly's series[10] there were 31 such girls as contrasted with only three examples in boys. In these girls there is the onset of normal puberty at an abnormally early age; otherwise the events of physiologic adolescence are in the proper order. Biologic evidence that this puberty is functionally normal may be adduced from the relatively large number of pregnancies in girls with this condition. Wilkins[18] reviewed the literature and found that out of 310 girls with constitutional sexual precocity there were 70 instances of pregnancy before 14 years of age. The successful pregnancy of Escomel's remarkable patient, Lina Medina, attests to the fact that constitutional precocious puberty may result in fertility in a female as early as five years of age. As in children with congenital adrenal hyperplasia, there is a period of rapid growth, after which growth ceases because of early epiphysial fusion. This results in some shortness of stature in the adult, but otherwise there appears to be no disability associated with this condition in adult life.

Diagnosis. As has been pointed out by Lloyd,[12] diagnosis of constitutional precocity in girls is based principally on the absence of detectable organic lesions and the finding of levels of urinary gonadotropin and evidence of estrogen secretion compatible with the degree of sexual maturation. The urinary gonadotropin technique as described by Kline-

felter et al.[11] is commonly used for the gonadotropin assay, and for the estimation of estrogen secretion the vaginal smear technique as is done by Papanicolaou laboratories has proved useful.

TREATMENT. As was mentioned in connection with constitutional precocity in the male, there is no rationale for the use of x-ray therapy or potent hormonal agents in the treatment of this condition. Parents should be made aware that these precocious girls are fertile.

The guides to case management previously recorded for sexually precocious males apply to the females, with two additions by Hampson and Money which apply strictly to girls:[8]

1. The girl with sexual precocity should be adequately briefed on the physiology and purpose of menstruation, much as though she were a normal preadolescent. Hopefully, this should be done before she begins to menstruate, and if possible the teacher or other school authorities should be prepared to meet this eventuality without panic.

2. Girls with constitutional sexual precocity should be told that their breast development is early, but is not abnormal. Hampson and Money[8] describe a girl with constitutional precocious puberty who was suffering from the comments made by her schoolmates about her enlarging breasts. When it was suggested to her that they might actually be envious of her breasts (a point which had never occurred to her), her morale took a distinct turn for the better.

ISOSEXUAL PRECOCITY DUE TO ADRENAL DISEASE

This is an extremely rare cause of sexual precocity in girls, and a number of the cases reported are doubtful ones. Jolly[10] lists a total of 20 cases described as such, of which several were without histological proof.

PRECOCITY DUE TO OVARIAN DISEASE

Granulosa Cell Tumor

Granulosa cell tumor appears to be the most common offender in this group of rare causes of female precocity, and even it is rather rare. Jolly[10] found that the largest series obtained in reviews of the literature was 31 cases. As Lloyd has recently emphasized,[12] any girl who has a rapid onset of precocity, who does not have elevated gonadotropin levels and whose vaginal smear indicated an intense estrogen effect should be presumed to have a neoplasm producing estrogens. Before any operative procedure is done, however, the possibility of accidental ingestion of estrogens should be thoroughly explored with the parents, since exogenous estrogen could also reproduce these findings[4] (see p. 885).

Other Ovarian Tumors

Sexual precocity in girls may also be caused by chorio-epithelioma and by teratomas of the ovary. Less than a dozen cases are known to exist in this group. These tumors are exceedingly malignant. A case of the latter follows:

CASE HISTORY. B.C., a white girl, was seen at the age of 8 years with the complaint of "hardness down in the stomach" of 1 week's duration. One month before admission the mother had noted that the girl's breasts had been enlarging and that there was some pubic hair. The parents had not noted any vaginal bleeding or discharge. One week before admission it was observed that her lower abdomen was "bloated." The mother felt the child's abdomen and found a hard lump about the size of an orange, at which time the child was hospitalized. The past history and family history are noncontributory. Physical examination revealed a well nourished white girl with a protuberant abdomen, breasts and pubic hair (see Fig. 13). There was definite breast development without pigmentation of the areolae. Fine axillary hair was present. The abdomen showed a nontender, firm, movable mass below the umbilicus, near the midline. The genitals revealed a moderate amount of pubic hair (see Fig. 14). There was pigmentation of the vulvar area. The clitoris was not enlarged. As is strikingly shown in Figure 14, the labia minora were hypertrophic and pouted out of the vulvar area like a rooster's comb. It is believed that this represents the effect of estrogen stimulation on this particular tissue.

Laboratory Data. Bone age was 10 years. The transverse colon was displaced upward when an x-ray examination was made. A vaginal smear stained by the Papanicolaou technique revealed an adult-type cellular pattern. Plasma 17-ketosteroids were too low to measure (normal for this age). Estimation of urinary gonadotropin by the laboratory

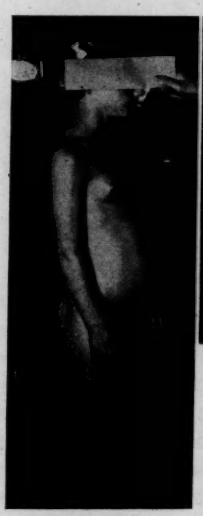

Fig. 13.

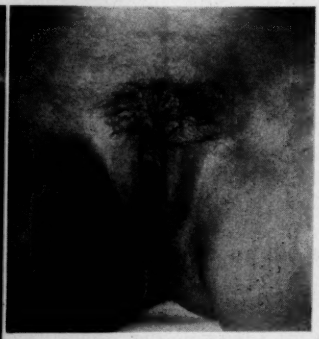

Fig. 14.

Fig. 13. Girl with teratoma of the left ovary, age 8 years.

Fig. 14. Genitals of girl with teratoma of left ovary. Note pubic hair and exuberant tissue of labia minora emerging from vulva. This is a specific effect of estrogen. Labia majora and clitoris (androgen influenced) are undeveloped.

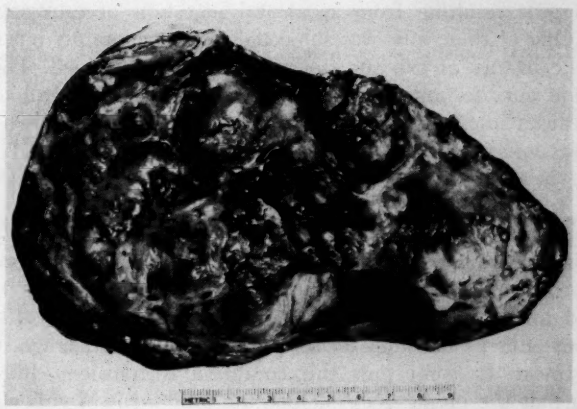

Fig. 15. Gross appearance of left ovarian teratoma from girl age 8 years.

of Dr. Charles W. Lloyd revealed greatly increased activity. At operation a large mass was found replacing the left ovary. Examination of the tumor after removal revealed a mass weighing 565 gm. which was composed of multiple small cysts, as shown in Figure 15. Histological examination revealed an ovarian teratoma showing intestinal epithelium, squamous epithelium, brain tissue and foci of dysgerminoma formation. The opposite (right) ovary, which had also been removed, showed ripening follicles.

Course. Over the next few years there was evidence of regrowth of the tumor, and the patient finally expired with a peritoneal cavity full of metastases slightly over 4 years later.

SEXUAL PRECOCITY IN THE FEMALE ASSOCIATED WITH CEREBRAL DISEASE

Most of the considerations which have been presented concerning this group of diseases in the male also hold true for the female. Although there is some evidence in the literature that cerebral disease as a cause of precocity is less frequent in the female, the series of cases compiled by Wilkins[18] and by Jolly[10] do not support this.

As was discussed in the section on male precocity, the McCune-Albright syndrome of sexual precocity, skin pigmentation and polyostotic fibrous dysplasia may or may not be properly assignable to the category of cerebral disease. Nearly all the reported cases of this syndrome are in girls. The numerous and diverse hypotheses as to the etiology of the McCune-Albright syndrome have been reviewed recently by Jolly.[10]

MISCELLANEOUS TYPES OF ISOSEXUAL PRECOCITY

Estrogen Ingestion

Cook et al.[4] have reported two cases of precocious sexual develop-

ment in girls resulting from accidental ingestion of estrogenic substances. One of these girls was subjected to an exploratory laparotomy before the history of exposure to stilbestrol was obtained. These authors point out the important physical finding that stilbestrol administration causes intense areolar pigmentation, an observation which led to the diagnosis in one of their patients.

Premature Development of Breasts

Certain girls show an early development of the breasts unassociated with any of the other manifestations of puberty. They do not have the advanced linear and osseous maturation of girls with constitutional precocious puberty, and they do not show any puberal changes in their vaginal smear. In some girls this condition is transient. Jolly[10] has observed that the nipple does not become prominent in girls with premature development of the breasts, whereas it does in girls with constitutional precocity.

Premature Development of Pubic Hair

Silverman et al. have described in detail 29 children who had sexual hair before the age of eight years.[15] There was only one boy in this group of cases. In the girls, coarse hair usually appeared first on the labia majora, next in the pubic region and lastly in the axillae. There was generalized hypertrichosis in only one case, and there was no evidence of true virilization in any of the cases. None of the patients had acne or deepening of the voice. The children tended to be taller than average, and their osseous maturation was one to four years ahead. The age when breast development and menarche occurred did not differ significantly from the normal. The urinary 17-ketosteroid excretion of these patients did not show any remarkable increase over normal.

This condition must be differentiated from virilizing adrenal tumor and from congenital adrenal hyperplasia, since both these latter conditions may have as the initial sign the premature development of pubic hair. If there are no androgenic manifestations except sexual hair and slightly increased somatic growth and osseous development, and if the urinary 17-ketosteroids are not especially increased beyond the normal limit for the age, the physician should be content to observe the patient at intervals over the next several years. These cases also do not have elevated urinary 17-ketosteroids and would exhibit a negative Allen's test for dehydroepiandrosterone. If the various lines of evidence indicate that the child is not suffering from early virilization due to hyperadrenocorticism, then the parents can be reassured that the condition is merely a variation in the normal pattern of development.

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NEWER KNOWLEDGE OF ADRENOCORTICAL DISTURBANCES

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Now, *here*, you see, it takes all the running *you* can do, to keep in the same place.—The Red Queen to Alice, in *Through the Looking Glass*.

GENERAL CONSIDERATIONS

Our new knowledge in this, or any other field, extends out into the unknown as we learn new and better ways of making measurements. In the field of adrenocortical metabolism much of our most recent information has come from measurements made on four different steroid molecules. These, depicted in Figure 16, are (1) aldosterone, (2) 17-hydroxycorticosterone or hydrocortisone (now often called cortisol), (3) dehydroepiandrosterone, and (4) androsterone. Probably progesterone should be in the list, because of the increasing evidence that it is implicated in the metabolism of the fetal adrenal cortex. Certainly Klein's important sodium-losing substance should be depicted, but its structure is not yet known for certain.[14]

Aldosterone

Chemical assay methods for aldosterone have just come into their own within the past year, and a great deal of activity is presently centering around analyses of urine samples of patients with this and that syndrome. Already one child with what appears to be something very much akin to congenital alkalosis with diarrhea has had its urine analyzed for aldosterone.[21] Alas, it was not elevated! A most illuminating

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finding has been made by Prader and colleagues at Zürich.[20] They measured urinary aldosterone excretion in young infants with the sodium-losing variant of congenital adrenal hyperplasia and found normal or even increased values. This immediately exploded any notion that these infants suffered from an absolute inability to synthesize aldosterone. Then these workers found that an older child with spontaneous regression of the excessive sodium loss had enormously increased urinary aldosterone excretion. There seems to be little question that this represents a compensatory overproduction of aldosterone serving to negate, at least in part, the sodium diuretic effect of the as-yet

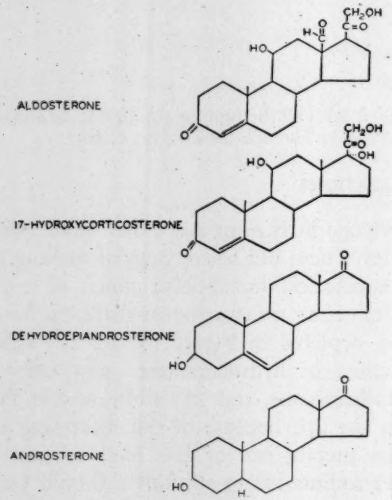


Fig. 16. Structural formulas of 4 of the most prominent metabolically active steroids in extracellular fluid.

elusive sodium-losing substance. The finding of Prader and colleagues now explains why the sodium-losers "get better" as they get older, and can be taken off desoxycorticosterone (DCA) therapy entirely by the second or third year of life.

A number of infants with the sodium-losing form of congenital adrenal hyperplasia have now been treated with the long-acting form of DCA (DCA trimethylacetate). Its great advantage is that it permits control of the excessive sodium loss by means of injections at monthly intervals, instead of daily, as with DCA in oil. Its administration is simpler than that of DCA pellets, which have to be inserted surgically and may become involved in a tissue reaction. The only real difficulty thus far en-

countered with DCA trimethylacetate is an occasional instance of abscess at the injection site. It is recommended that the gluteal region be given a thorough surgical preparation before such an injection is made. The vial containing the DCA trimethylacetate also should be agitated carefully for a prolonged period before the suspension is withdrawn into a syringe.

There seems to be little doubt about the finding by Luetscher and colleagues[15] and by McCall and Singer[16] that there is an increased urinary excretion of aldosterone in children with the nephrotic syndrome. Of course nobody knows what this means, but it undoubtedly means

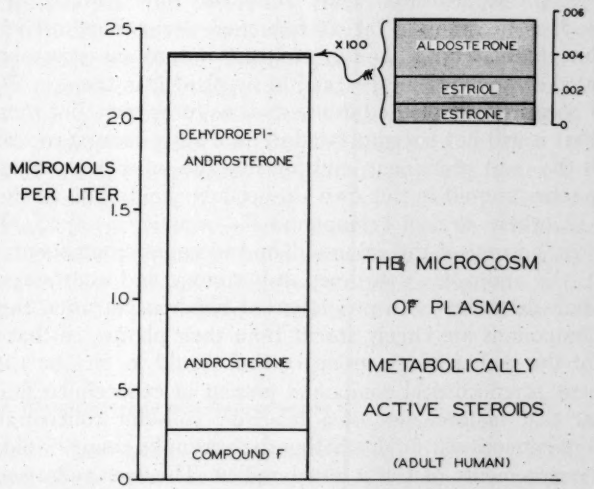


Fig. 17. Gamblian diagram of metabolically active steroids of plasma.

something. There seems to be a lull just now in the offensive in this field. In the meantime we will all adjust our Merlin robes and continue our cabalistic therapy of the nephrotic syndrome. Or at least we can continue it until the wily sodium-losing substance becomes available for therapeutic use.

Before leaving aldosterone and related subjects, it should be pointed out that the *absolute* quantities of aldosterone available for measurement in body fluid are exceedingly small and hamper investigative efforts. This is graphically shown in Figure 17, which plots the plasma concentrations of several metabolically active steroids. Observe that the steroids are expressed on a molar basis, so that a Gamblian-type of diagram can be made. Aldosterone occupies only a portion of that thin,

shaded line at the top of the column, homologous to the position of free hydrogen ion at the top of Gamble's charts. It is in the same micro-microcosmic league with estriol and estrone. The amount of plasma required to make an estimation of its concentration is sufficiently large so that the only measurements made thus far have been on adults. Further, certain technical difficulties in the organic synthesis of aldosterone have held up the production in large quantity of the steroid itself, thus impairing widespread clinical investigative trials.

Cortisol (17-Hydroxycorticosterone; Hydrocortisone)

The second segment of Figure 16 is this now familiar structural formula. It is becoming a bit old-fashioned to mention cortisol, what with the pharmaceutical houses emitting a constant stream of new substituted compounds, all designed to supplant it in therapy. Whether cortisol is entirely supplanted in *use* remains to be seen, but there is no doubt that it will not be supplanted in *us*. This is because cortisol is by all odds the most prominent, and possibly the most important, carbohydrate-active steroid in our own extracellular fluid. This is shown in Figure 17, where cortisol (compound F) occupies a respectable position at the bottom of the column. The two largest components of the column, the androgens dehydroepiandrosterone and androsterone, are not carbohydrate-active. In preadolescent children, however, these two latter compounds are largely absent from their plasma, so that among much of the pediatric age group cortisol would in fact be the *most* prominent adrenocortical compound present in extracellular fluid. It is apparent that maintenance of a relatively constant concentration of cortisol in extracellular fluid, whether the person be young or old, is one of the requirements of the internal milieu. The two androgens mentioned are scarcely present in plasma during childhood, predominate quantitatively in plasma during young adulthood, and probably decrease in old age. The blues song says that "A woman is a sometime thing," and that adage may also be applied to the plasma androgens. Cortisol in plasma, however, maintains its equanimity throughout life, barring adrenal disease or pregnancy, and provides an environment for the orderly functioning of carbohydrate metabolism.

Pregnancy was mentioned as an exception to the foregoing statement. The metabolism of cortisol during pregnancy and in fetal development is a complicated matter. Gemzell made the important observation that the cord plasma corticoids of babies born by vaginal delivery were significantly higher than similar values on the cord plasma of babies delivered by cesarean section.[10] Migeon and colleagues have confirmed this observation and extended it considerably. The latter group have found that cortisol passes from the maternal to the fetal circulation via

the placenta in constant ratios.[19] Their data are interpreted to indicate that the fetus is producing little if any cortisol at term, and that cortisol is transferred from mother to baby in definite proportions. More recently these workers have investigated the peripheral utilization of cortisol in the pregnant woman, and have found that the increase in free plasma cortisol observed near term is apparently related to a slower rate of catabolism of cortisol rather than to a more rapid rate of its production.[17]

The now well verified observation that babies born by vaginal delivery have an appreciably higher plasma level of cortisol than babies born by cesarean section raises some interesting points for speculation. The evidence that the developing fetus biosynthesizes essentially no cortisol indicates that the fetus' first "taste" of cortisol is probably that which passes through the placenta during vaginal delivery. We know from the studies of Klein that the newborn is not able to raise its own plasma concentration of cortisol to visible levels until several days of life have passed. Therefore one wonders whether this "shot" of cortisol the infant gets as it negotiates the birth canal might not be there for a purpose. The baby born by cesarean section definitely misses out on it. Since babies born by cesarean section tend to have a greater morbidity than babies born normally, it might be interesting to see what a single injection of 25 or 50 mg. of hydrocortisone hemisuccinate right after birth would do, if the morbidity results were evaluated on a statistical basis.

Dehydroepiandrosterone and Androsterone

These are the lower two compounds shown in Figure 16, and are the only known androgens in human plasma. Evidence suggests that the dehydroepiandrosterone is derived from the tissue of the adrenal cortex; much or all of the androsterone may be gonadal in origin. They are both chemically designed as 17-ketosteroids. The difference between the two molecules can be seen to be only the spatial orientation of the OH group at the 3 position and the presence or absence of the double-bond between carbon atoms 5 and 6.

As previously described, these plasma compounds have their ups and downs in the course of normal human development. The newborn infant's plasma may have a greater concentration of these steroids than does that of the adult, but the values fall rapidly during the first week of life to low or absent values. Not until beginning adolescence do the values of these steroids become appreciable in plasma, and then they rise until they attain the concentrations depicted in Figure 17. These values then are maintained for most of adult life (again excepting adrenal disease and pregnancy).

The original identification of dehydroepiandrosterone and androsterone as the two androgens of human plasma was made by Migeon and Plager.[18] Figure 18 shows additional support for their finding. The figure shows spectrophotometric curves of the Allen reaction for dehydroepiandrosterone. The top curve was made from a purified residue from acid-hydrolyzed, chromatographed, umbilical cord venous plasma which had been subjected to the Allen reaction. The middle curve was similarly made from a mixture of 20 micrograms each of pure androsterone and dehydroepiandrosterone. The bottom dotted curve was made from pure dehydroepiandrosterone alone (androsterone shows no peak in this reaction at 600 millimicrons). The result shows that a curve similar to that found in cord plasma can be obtained by the reaction run on such a mixture of these two pure androgens.

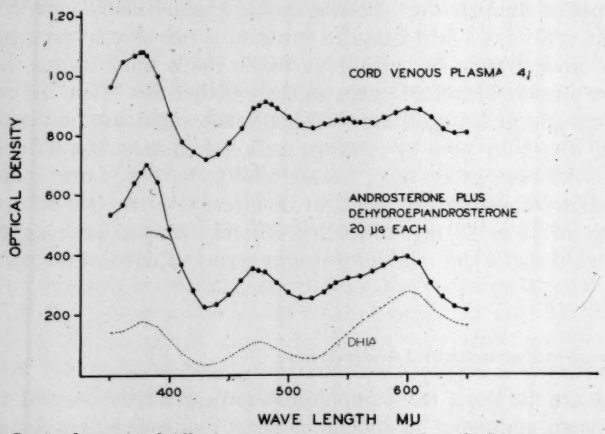


Fig. 18. Spectral curves of Allen's reaction on extracts of cord plasma compared with curves on pure steroids.

Newborn infants with congenital adrenal hyperplasia have been found to have values for plasma 17-ketosteroids (the androgens referred to above) as high as 325 micrograms per 100 ml., considerably higher than in the normal newborn.[9] The range for the normal newborn may be seen by consulting Figure 19.[7] In that figure the plasma 17-ketosteroid values for the normal newborns are represented as open "goose-eggs" along the ordinate. Urine 17-ketosteroid values are also shown to demonstrate the striking difference between the plasma values of 17-ketosteroids and their urinary excretion in the newborn. The "goose-eggs" with a P on top are the values for premature infants, who are seen to have very much greater concentrations of plasma 17-ketosteroids than the full-term infants. This phenomenon in premature infants has not been explained.[7]

The black dots in the transverse band of Figure 19 are values either for normal adults or for patients with hyperadrenocorticism. All the black dots with urine 17-ketosteroid values of less than 20 mg. per day are normal adults. Then there is a group of black dots with urine 17-ketosteroid values between 20 and 50 mg. per day. All these were children with untreated congenital adrenal hyperplasia. The topmost black dot (urine 17-ketosteroids over 200 mg. per day) represents a female pseudohermaphrodite, age 12 years, untreated. The next to the topmost black dot represents an adult woman with a virilizing adrenal tumor prior to operation. It is obvious from these data that the plasma

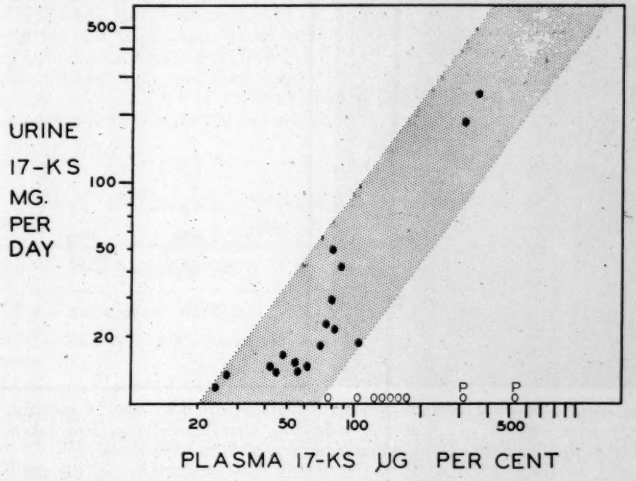


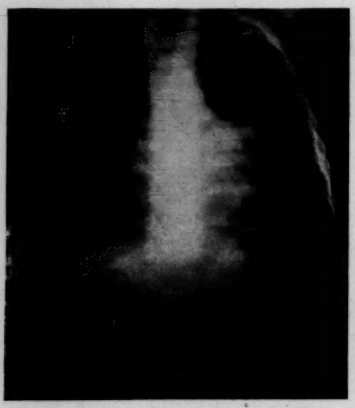
Fig. 19. Relationships of urinary 17-ketosteroids to plasma 17-ketosteroids. O = normal, full-term newborns; $\frac{P}{O}$ = prematures; • = normal adults and hyperadrenocortical patients (see text).

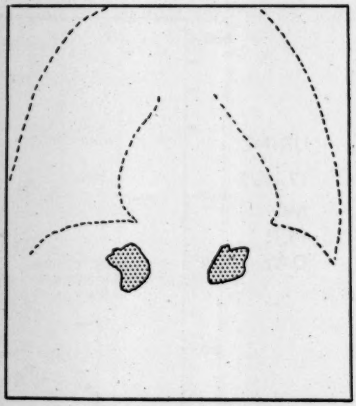
androgens do indeed undergo profound variations at the time of birth, in the instance of prematurity and especially in cases of hyperadrenocorticism. There are also changes of these steroids at adolescence, during Addison's disease and during pregnancy, but space does not permit presentation of these data.

HYPOADRENOCORTICISM IN INFANTS

True Addison's disease (hypoadrenocorticism associated with absence or destruction of adrenal tissue) is extremely rare in young infants. This is not to be confused with excessive sodium loss due to congenital

adrenal hyperplasia, in which the sodium loss occurs presumably due to the overproduction of a sodium diuretic hormone. Williams and Robinson have recently reviewed the authenticated cases of Addison's disease in infants in the English literature and found only nine examples, to which they added seven cases.[25] At autopsy in six of these cases adrenal hypoplasia was found, and in one case adrenal cysts were found. The present author has observed three such cases, two of which showed bilateral calcification of the adrenal glands. Since this syndrome has received little attention in this country, the case histories of three patients seen at this Center will be presented as illustrative examples.





Figs. 20, 21. Bilateral adrenal calcification of patient S.K., age 15 months. Note relatively large size of calcifications, indicating that calcification had taken place probably in the newborn period, when gland was of fetal adrenal size.

CASE HISTORY I: CALCIFIED ADRENALS PROBABLY DUE TO BIRTH TRAUMA; REPEATED CRISES WITH INFECTION; NO PLASMA CORTICOIDS NORMALLY. S.K., a white boy, had been prematurely born, his mother having gone into labor at 7½ months of gestation. The position of the baby was transverse, with a footling presentation. After a breech delivery the infant responded poorly to resuscitation. Birth weight was 4 pounds 7 ounces. The right foot and lower leg were edematous and cyanotic, presumably as a result of the traction applied. After 15 minutes of resuscitation the baby cried well and thereafter had an uneventful neonatal course. He remained in the hospital until 6 weeks of age, at which time he weighed 5 pounds.

At age 11 weeks a right inguinal herniorraphy was performed without incident. At age 15 months the patient had a low grade fever with restlessness and finally dyspnea. When he was brought into the hospital, his fever was above the 106° F. mark on the rectal thermometer. Several observers noted unusual pigmentation of the skin. He was retracting and in acute distress. Crepitant rales were heard throughout both lung fields. X-ray study of the chest revealed consolidation of the left midlung field. At that time it was noted that *there was massive bilateral adrenal calcification* (see Figs. 20, 21). The x-ray finding of calcified adrenals was not made until after the patient had begun to show definite improvement with chemotherapy. The serum sodium was 127 mEq. per liter and the serum potassium 3.4 mEq. per liter. As the patient improved, both his serum sodium and potassium values rose. At the time of his discharge from the hospital

several days after the first serum measurements had been made, the serum sodium was 135 mEq. per liter and the serum potassium 4.2 mEq. per liter. After this episode of pneumonia, serum sodium and potassium determinations were done weekly for 2 months. Findings were normal except on one occasion when the serum sodium was 129 mEq. per liter and serum potassium 5.4 mEq per liter. There were no signs or symptoms at this time. It was believed that the observed electrolyte findings were not entirely typical of the sodium-potassium defect in Addison's disease, but the disproportionately severe reaction to the pneumonia suggested some element of adrenocortical deficit.

Three months later the infant was again admitted because of difficulty in breathing. There was consolidation of the right upper lung field. Antibiotics and intramuscular hydrocortisone were given. Once again the infant showed a disproportionately severe reaction to the pulmonary infection, with fever to 103° or 104° F. each day for 5 days. Serum sodium was 138 mEq. per liter and serum potassium 4.4 mEq. He eventually responded to treatment. After recovery from this infection, further investigation of his adrenal status was carried out. ACTH was given intravenously, 10 units per square meter in a single dose. Blood total eosinophils and serum 17-hydroxycorticosteroids were measured before ACTH and 2 hours later according to the technique of Dr. Robert Klein. The results are shown in Table 7. A fasting blood glucose was normal. By this time (age 21 months) the skin pigmentation had become obvious with areas of increased pigmentation especially over the ankles and wrists.

TABLE 7.

CASE NO. 1	17-HYDROXYCORTICOSTEROIDS μg./100 ML. SERUM	EOSINOPHILS PER CU. MM.
Before ACTH	0	900
Two hours after ACTH	24	944

Ten I.U. ACTH (Parke-Davis #35-98-1) per square meter were given rapidly intravenously.

Comment. It would appear that this infant suffered trauma to his flanks during birth and that adrenal hemorrhage probably occurred at that time, with subsequent calcification of the adrenal glands. The skin pigmentation, adverse reaction to respiratory infections, and absence of circulating 17-hydroxycorticosteroids all suggest adrenal insufficiency. The failure to detect the classic addisonian defect in serum sodium and potassium concentrations suggests that the infant's adrenal hypofunction is more likely related to a relative inability to produce corticosteroids than to any defect in the production of aldosterone. The fact that intravenous ACTH was able to elicit an outpouring of 17-hydroxycorticosteroids in this patient further suggests that the defect is only partial. This infant has not yet been placed on constant maintenance therapy. Hydrocortisone has been given during episodes of infection, but not otherwise.

CASE HISTORY II: CALCIFIED ADRENALS OF UNKNOWN CAUSE; REPEATED CRISES WITH INFECTIONS; HYPOGLYCEMIA; NORMAL PLASMA CORTICOIDS WHEN NOT STRESSED. J.C., a white, male baby, was the result of an uncomplicated pregnancy with normal delivery. The birth weight was 5 pounds 10 ounces. For the first 11 months of life the developmental course was entirely uneventful. At age 11 months he had a mild

coryza and a dry cough. There was no fever. This went on for 6 days, at which point he was seen for a regular well-baby checkup, and "bronchitis" was noted. Achromycin was prescribed, and the infant improved in the succeeding 4 days. On the morning of the fifth day the mother noticed that the child was having generalized convulsions and that the lips were cyanotic. He was brought to the hospital, where it was found that he had a fever of 103.4° F. and was having generalized clonic convulsions. There had been a brief period of apnea en route to the hospital. Laboratory data showed a white cell count of 5600, with the rest of the hematological examination normal. Cerebrospinal fluid showed 33 mg. per 100 ml. of protein and 89 mg. per 100 ml. of sugar. Cultures of nose and throat showed normal flora; cultures of blood and cerebrospinal fluid showed no growth. Chest x-ray showed clear lung fields and a normal heart. *There was calcification of both adrenal glands.* There continued to be small twitchings of the lower extremities and the left arm for a short time after admission, but with phenobarbital sedation this ceased. The child's fever spiked to 103° F. on the second day and to 104° on the third day. There were still no significant findings. On the fourth day of admission he broke out in a generalized rash, and the fever subsided simultaneously. It was concluded that the infant had had severe convulsions during the early, febrile stages of roseola infantum.

Six months later the mother discovered the child to be totally unresponsive one morning in bed at 8:30 a.m. He was examined shortly thereafter by his pediatrician, who noted that he was completely flaccid, unresponsive and areflexic, and that he had trismus. The infant was brought to the hospital immediately where, on admission, he was found to be afebrile and still unresponsive. There was generalized flaccidity together with persistent trismus. A fasting blood sugar drawn immediately after entry was 65 mg. per 100 ml. Lumbar puncture yielded clear fluid with no increase in pressure. There were no cells and a negative culture. Cerebrospinal fluid protein was 25 mg. per 100 ml. and sugar was 30 mg. Ten units of ACTH per square meter were given intravenously. The total eosinophil count before the intravenous injection of 10 units per square meter of ACTH was 100 per cubic millimeter and 2 hours after injection was 89 per cubic millimeter. X-ray examination of the abdomen, knees, wrists and skull was normal. Serum potassium was 5.1 mEq. per liter; sodium, 137 mEq.; phosphorus, 5 mg. per 100 ml.; calcium, 8.2 mg.; nonprotein nitrogen, 34 mg. per 100 ml.

At age 16 months the infant had a fever of 102.6° F. with evidence of pharyngitis. At 6 a.m. of the day of admission he awakened apparently well, but within about 15 minutes became drowsy and unresponsive. He was brought immediately to the hospital, where he was found to be quite drowsy, but could be easily aroused, after which he readily had lapses into a deep sleep. He had an injected pharynx and a left-sided otitis media. Temperature was 98.6° F. Fasting blood sugar drawn immediately on arrival was 50 mg. per 100 ml. White blood cell count was 7600 per cubic millimeter, with the rest of the hematological data normal. Nose and throat cultures showed normal flora. The child ate well later on the day of admission and became somewhat less lethargic during the afternoon of the first day. On the second day there was no evidence of lethargy. A fasting blood sugar was done after an 18-hour fast just before discharge, and a value of 80 mg. per 100 ml. was obtained. A specimen of serum for the measurement of 17-hydroxycorticosteroids was obtained on a day when the child was afebrile and symptom-free. The value was 15 micrograms per 100 ml., which is normal.

Comment. This child with bilaterally calcified adrenals had crisis-like episodes associated with infections in a manner similar to Case I. In this case, however, the most convincing laboratory finding was hypoglycemia. There is no apparent explanation for the different pattern of metabolic behavior shown by these two cases with calcified adrenals.

CASE HISTORY III: HYPOPLASTIC ADRENALS OF UNKNOWN CAUSE; RESPONSE TO HORMONAL THERAPY; SUDDEN DEATH AT AGE 4 WEEKS. W.L., a white, male infant, was born after an uneventful pregnancy and an atraumatic low-forceps delivery. The birth weight was 8 pounds 2½ ounces. The infant did well in the neonatal period and

was discharged from the nursery with a weight of 7 pounds 10 ounces. At home the mother reported that the baby did poorly and frequently refused an evaporated milk formula. There was gradual loss of weight with alternating periods of irritability and sleepiness. There were no convulsions or diarrhea. Two days before hospital admission the child began to vomit intermittently.

At the age of 19 days the infant was brought into the hospital. Physical examination showed a marasmic infant with a weight of 6 pounds 8 ounces. The baby refused feedings and had to be placed on parenteral fluid therapy. Subdural taps revealed no fluid. On the second hospital day there was further vomiting, and the infant had a loose yellow stool. Fever to 102.8° F. developed on the third hospital day and persisted for the rest of the hospital stay. The infant was given intramuscular penicillin and streptomycin, in spite of which the fever continued. Stool and throat cultures showed normal flora; blood and cerebrospinal fluid cultures showed no growth. Culture from the mouth for monila was negative. By the sixth hospital day the infant did not appear to have improved. The skin color was poor, and there was respiratory difficulty. On the following day serum measurements revealed the following findings: sodium, 100 mEq. per liter; potassium, 7.7 mEq.; and chloride, 70 mEq. A tentative diagnosis of hypoadrenocorticism was made. Three milligrams of desoxycorticosterone acetate (DCA) and intravenous saline solution were given, which appeared to improve the baby's color. Additional treatment was made with whole adrenal extract. By the tenth hospital day the baby had become almost afebrile, and the color was good. The following measurements were made at that time: serum sodium, 150 mEq. per liter; potassium, 3.1 mEq.; chloride, 108 mEq.; inorganic phosphorus, 5 mg. per 100 ml.; calcium, 8 mg. The dramatic change in the serum and potassium was interpreted as the result of overtreatment with sodium chloride, adrenal extract and DCA. The baby was then placed on oral feedings and appeared to do well. Since there was a possibility that this male infant might have the sodium-losing form of congenital adrenal hyperplasia, measurement of concentrations of 17-ketosteroids was made in plasma and urine. There was no measurable concentration of 17-ketosteroids in plasma, and two urine specimens showed 1.1 mg. and 2.0 mg. of 17-ketosteroids respectively per 24 hours. These values made the possibility that this infant had congenital adrenal hyperplasia most unlikely.

On the fourteenth hospital day the baby was found dead in its crib. There had been no known convulsions, and the baby had been apparently well when previously seen. At the time of autopsy the infant weighed 6 pounds 1 ounce. There was evidence of aspiration of some formula into the trachea. There was mesenteric adenitis in the region of the small intestine. *The adrenals were grossly small and together weighed only 1.1 gm.* There were no other remarkable gross findings.

Comment. Unlike Cases I and II, this child did not have calcified adrenals, but rather had hypoplastic adrenal glands. It will be recalled that there is a steady fall in total weight of the adrenal glands during the first several weeks of life, during which time the transitional fetal zone is collapsing. After this primary phase there is a secondary phase of increasing adrenal weight, during which time the adult-type cortex is elaborated. It may be that this infant lacked whatever mechanism is necessary to initiate this secondary phase of adrenal proliferation.

HYPERADRENOCORTICISM IN INFANTS AND CHILDREN

General Considerations

The three principal categories of hyperadrenocorticism in infants and children are (1) congenital adrenal hyperplasia, (2) virilizing adrenal tumor, and (3) Cushing's syndrome (non-neoplastic and neoplastic).

The conditions are listed in decreasing order of frequency, congenital adrenal hyperplasia being by all odds the most frequent in occurrence. Since the adrenal cortex secretes an imposing and at times confusing array of steroids, the physical manifestations of their physiological effects depend upon what pattern of steroids is being produced at a given moment. There is hardly a better example of the specificity of molecular structure in conditioning physiological effects than the different syndromes caused by disordered adrenocortical steroid production.

Congenital Adrenal Hyperplasia

There have been a number of new contributions to the knowledge of this condition within the last few years. As is now well known, early

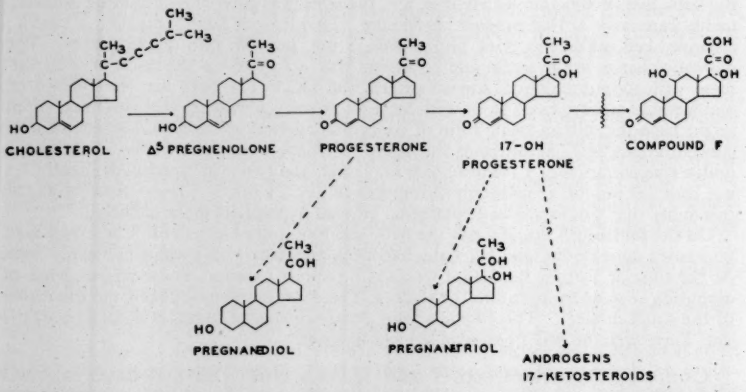


Fig. 22. A possible mechanism of the metabolic abnormality in congenital adrenal hyperplasia. (From A. M. Bongiovanni, W. R. Eberlein and J. Cara: *J. Clin. Endocrinol. & Metab.*, Vol. 14.)

in 1950 Bartter and colleagues[1] and Wilkins and colleagues[24] independently found that the administration of cortisone suppressed urinary 17-ketosteroid excretion in patients with congenital adrenal hyperplasia. Bartter and colleagues brilliantly postulated that "the primary defect in this syndrome is the decreased production of 'sugar' hormone by the adrenal cortex in response to ACTH."[2] This hypothesis has been entirely supported by subsequent work.[13, 22] It has been possible to offer long-term, successful medical therapy to children with congenital adrenal hyperplasia.[23] More recently activity has centered on attempts to localize the site of the error in the intermediary steroid metabolism of these children. Figure 22 shows a schema proposed by Bongiovanni

et al.[4] The figure demonstrates that with such a block to the biosynthesis of compound F (cortisol), there is a concomitant piling up of other metabolites. There now is evidence that the metabolic block may take place at different locations in the metabolic steroid pathway.[3]

GENETICS OF CONGENITAL ADRENAL HYPERPLASIA. Ever since the diagnosis of this syndrome has been possible it has been noted that more than one sibling of a family was often affected. It had also been observed that if one child in a sibship was a sodium-loser, all the other affected siblings would be sodium-losers. Figure 23 shows the family trees of two such sodium-losing families. It will be noted from this figure that collateral branches of the families showed no evidence of congenital adrenal hyperplasia. This is the case almost without exception. This is, of course, the pattern which one expects to obtain if the disease is a

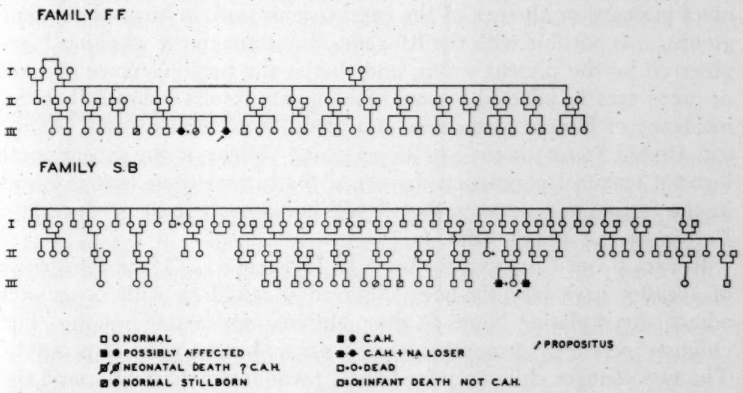


Fig. 23. Two kindreds with congenital adrenal hyperplasia of the sodium-losing type.

mendelian recessive trait. It seems important to point out this fact, since the statement is often heard that such-and-such a condition is not "familial" (i.e., not genetically determined) because there is no family history of it in previous generations. This statement is incorrect, since a negative family history for the disease in question is just what one expects to find if the condition is a mendelian recessive.

There is increasing interest on the part of parents in understanding the available facts concerning the genetic aspects of a disease such as congenital adrenal hyperplasia. It is, therefore, important for the physician to help them in grasping the genetic mechanisms involved.

For instance, bringing out the mere fact that both the mother and father are equally "responsible" (genetically) for the abnormality of congenital adrenal hyperplasia may serve a good purpose in equalizing guilt feelings. Parents also seem to appreciate knowing how frequent the

heterozygous gene is in our population (1 heterozygous per 128 persons).[5] This helps to make them feel a little less "queer." This writer, in such a discussion, has found it helpful to draw two circles on a piece of paper. One represents a randomly sampled group of 128 people, including the mother. It becomes obvious to the parents how fortuitous is was that they, the only heterozygotes in the two groups, happened to get together. This is further supported by the relative rarity of the syndrome: 1 per 67,000 live births.[5] An open discussion of the genetics of this syndrome with parents, using only the few statistical data quoted above, seems to relieve a certain degree of tension. Possibly just the knowledge that this represents one or more of the many mutations that the human race has been living with for thousands of years is helpful.

In what geographical location did such a mutation first occur? Unfortunately for us, there is yet no simple blood test to determine the exact presence or absence of the heterozygous state in large population groups, as is possible with the Rh gene. One straw in the wind has been observed by the present writer, and that is the preponderance of blue or green eyes in affected persons. Preliminary results indicate that the incidence of blue or green eyes in a group of affected persons (northeast United States) is close to 75 per cent.[9] Whenever the geographical locus of maximal population density of the heterozygous trait is found in the future, one suspects that it will be somewhere in northwestern Europe or the British Isles.

Rubeola and Congenital Adrenal Hyperplasia. Three fatal cases of measles have recently been observed in children with congenital adrenal hyperplasia.[8] None of these children was a sodium-loser. The children were age 14 months, seven years and eight years respectively. The two younger children were female pseudohermaphrodites, and the oldest was a male with virilization. The youngest had never received any cortisone, the next child was being treated, and the oldest was receiving a low dose of cortisone (25 mg. orally every other day). All three children died abruptly during the course of rubeola. Autopsy studies revealed no evidence of adrenal atrophy; in fact, the adrenal glands were large. The older boy's two adrenal glands weighed together 62 gm. Histochemical studies revealed that there was almost complete depletion of the sudanophilic material in the adrenal cortical tissue of the two children. These findings suggest that the adrenal cortices of these three children were undergoing maximal endogenous stimulation during the course of their measles. This is consistent with previous observations made on children during the course of measles which support the concept that rubeola has an unusual potency in stimulating the adrenal cortex. It is also known that children with congenital adrenal hyperplasia show a paradoxical adrenal response to exogenous ACTH (sodium loss rather than sodium retention). Thus

it is conceivable that the intense stimulation of the adrenal cortex caused by measles may result in a specific response unfavorable to the patient with congenital adrenal hyperplasia.

The foregoing situation is not to be confused with the fatal cases of chickenpox which took place during treatment with cortisone.[12] In the chickenpox cases it would seem that there was suppression of adrenal function by cortisone in children with otherwise normal adrenal cortices. This is an entirely different metabolic setting from that found in the child with congenital adrenal hyperplasia, who requires replacement treatment with cortisone or hydrocortisone.

It is suggested that children with congenital adrenal hyperplasia who are exposed to rubeola receive modifying doses of gamma globulin, and that they be hospitalized and observed with great care once they start coughing and become febrile in the course of their modified measles. They may need additional doses of cortisone or hydrocortisone above their ordinary daily dose requirement.

Other Forms of Hyperadrenocorticism

Virilizing adrenal tumor in children is discussed to some extent in the clinic on Isosexual Precocity in Infants and Children (p. 879). No real clue has yet been obtained as to the metabolic error present in these cases, except the obvious overproduction (or underconsumption) of dehydroepiandrosterone. The literature pertaining to this disease entity has been reviewed elsewhere.[6] Much the same story obtains for Cushing's syndrome in children, although it has been observed that there is a different pattern of plasma corticoid response to ACTH in these patients.[11]

The author is indebted to Drs. William D. Alsever and Stuart A. Pomeroy for permission to report their patients S.K. and J.C. Thanks are due to Mrs. Walter A. Lipfert and Mrs. Betty Lawrence for preparing the figures. The plasma corticoid determinations reported were done through the courtesy of Dr. Robert Klein.

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INTERSEXUALITY

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Basic patterns of sexual differentiation begin to emerge as individual patients are studied, experiments are correlated, and tests and techniques are perfected. Sexual development is a continuum, and aberrations from normal paths express themselves in infinite variations. By utilizing chromosome analysis, however, we can (perhaps somewhat arbitrarily) divide intersexual patients into genetic males and genetic females (Fig. 24). Intersexual development in the gonadal male fetus can be arbitrarily labelled feminization, and that in the female as masculinization. Further, we can postulate that the male embryo may be actually feminized (indirectly by the diminished organizer activity of the testis), or may *appear* to be feminized, because of a mutation or blighting effect during the embryonic formation of the male genitals. For the female embryo to become intersexual, active masculinization is required. This can be brought about by the direct action of male hormones from the adrenals as well as by the arrest of female characteristics through blighting, with resultant overgrowth of male components. These hypotheses give us a working classification (Fig. 25).

The three main divisions of this classification arise from laboratory experiments (blight, testicular excision and androgen administration), but also can be illustrated by many clinical variants. These critical tests on animals expose certain etiologic mechanisms which perhaps underlie some of the observed types of human intersexuality.

BLIGHT

Stockard's experiments[22] reveal the fundamental mechanism by which blighting produces anomalous development. The egg of the

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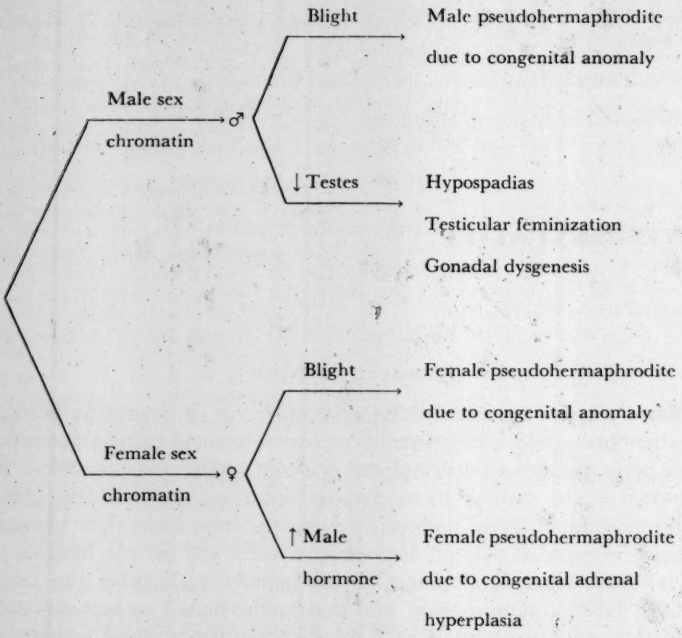


Fig. 24. Classification of intersexual patients as genetic males or genetic females.

marine minnow, Fundulus, if cooled at a certain stage of development, will form a perfect twin (Fig. 26), but, if cooled at a later time, will form instead an imperfect second embryo. With the use of temperature, chemicals, anoxia and other agents, Stockard and others have been able to produce fusions, duplications, local overgrowth and suppression of the several organ systems.

The human fetus similarly can be affected by changes in maternal metabolism or by variations in the placental circulation. If these blight-

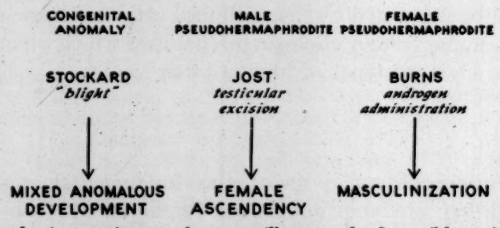


Fig. 25. Three classic experiments chosen to illustrate the 3 possible main mechanisms producing human intersexuality.

ing influences occur at the exact moment of ascendancy of the female urethral plate, the phallic portion may close over to form an anomalous penile urethra.

Of course, the "blight" may not be so simply caused. Since the noxious agents in many instances appear to act locally, and since the resulting anomalies follow certain patterns, it is likely that genetic factors are at work. Genetic effects may be produced by mutation or by the coincidence of recessive traits.

If a temporary blight occurred before gonadal differentiation, monsters with genital abnormalities would be expected. Blighting during

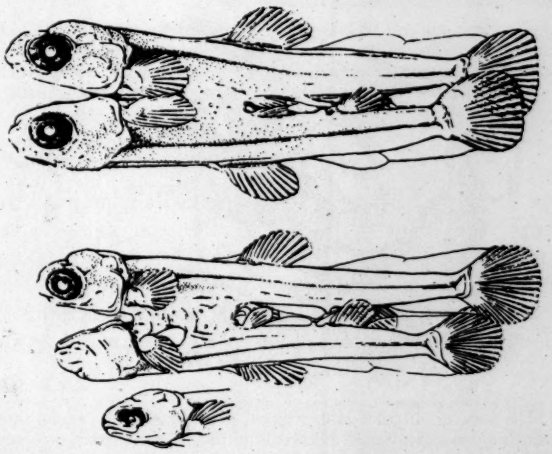


Fig. 26. Twinning in fishes from cooling during early development. (From Stockard.[22])

gonadal development could produce gonadal retardation, which secondarily would cause intersexual development (as we will see under Suppression of Male Gonads).

Conceivably, any genital anomaly is possible. Actually, only a few major patterns appear: (1) true hermaphroditism, with development of both male and female gonads, (2) intersexuality of the vaginal urethra type, with phallic urethra, (3) extreme anomalous development, approaching monster formation, with gross genital and other malformations.

True Hermaphroditism

The internal and external genitals of persons with gonads of both sexes (true hermaphrodites) may be predominantly male or female

(Fig. 27). Patients with a testis and ovary in separate gonads are more unusual than those with mixed gonads. The chromosomal sex presumably may be male or female. The basis for this true mixture of male and female could be developmental arrest during the time of organization of the gonadal tissue (*cf.* Bidder's organ in the chicken) or could be anomalous twinning. In addition, a mosaic structure must be considered. The possibility also exists that true hermaphroditism is the result of varying degrees of male gonadal influence (*cf.* testicular feminization).

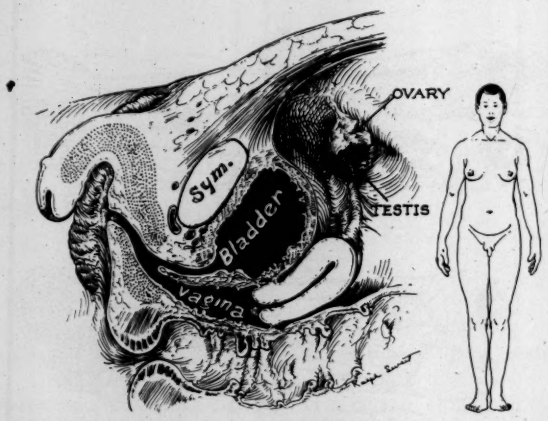


Fig. 27. Diagram of internal and external genitals in true hermaphroditism. The characteristics of gonadal intersex hermaphroditism are ovotestes or ovary and testis, with variable intersexual development of the genitals.

Female Intersex, Vaginal Urethra Type[15]

If arrest occurs just as the activity of Müller's hillock is ascendant over the pars phallica of the urethra, growth of the male elements of the urethra then predominates. Such an arrest results in (1) a slightly cranial location of Müller's hillock, which places the urethral meatus within the vagina, and (2) alteration of the normal development of the pars phallica, so that the labia minora are agglutinated; the clitoris enlarges and may contain an accessory (masculine) urethra. Figure 28 shows one of two such children we have studied. An excision of the clitoris was done and the labia minora were folded in to bring the vaginal urethra to the surface. The girls have subsequently developed normally.

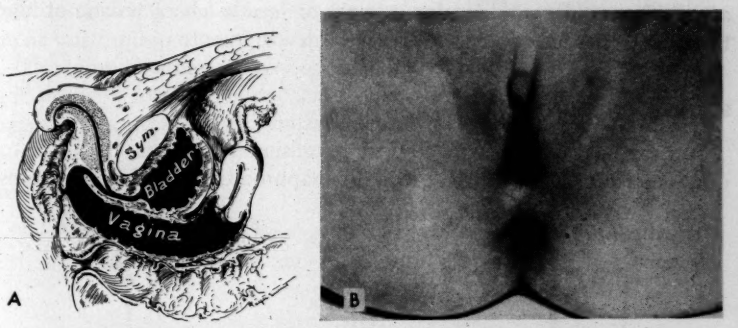


Fig. 28. A, Characteristics of female intersex, vaginal urethra type: normal ovaries and adrenals; muellerian ducts imperfect in descent and fusion; atypical masculinization of urogenital sinus. *B*, External genitals of female child with a urethra coursing through the phallus, and a second urethra emptying into the vagina.

Intersexual Appearance with Multiple Anomalies

This rare form might be expected in newborn children who have many gross anomalies, especially of the urinary tract. The "arrest" here is considerable, and there is a consequent greater derangement. Figure 29 shows a typical case: a phallic urethra was accompanied by renal hypoplasia, imperforate anus and rectovesical fistula.

In *summary*, an appearance of intersexuality may be produced by

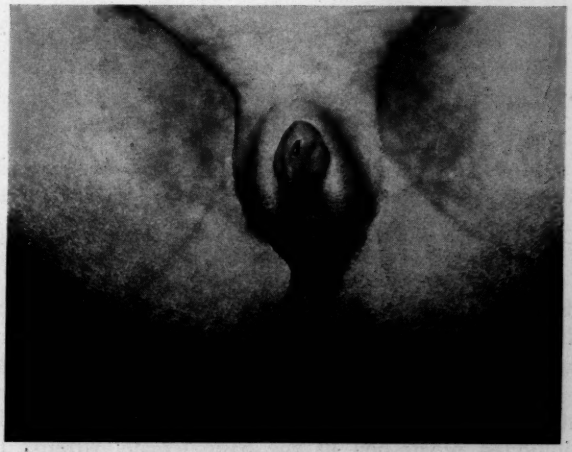


Fig. 29. External genitals of female child with multiple anomalies, showing urine issuing from the phallic urethra.

arrest of an ordinarily dominant male or female characteristic at the time of its normal ascendancy in fetal development.

SUPPRESSION OF MALE GONADS

Jost's experiments[17] with testicular excision in rabbits are basic to our understanding of male pseudohermaphroditism. In his ingenious

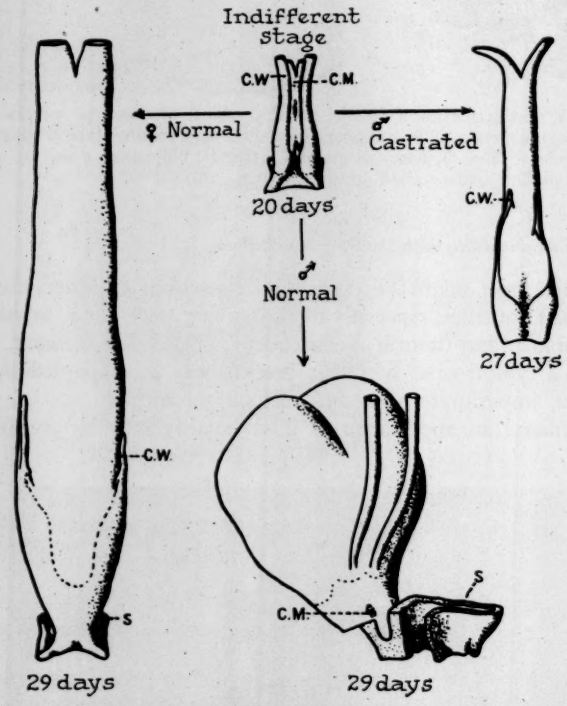


Fig. 30. Genital development in the rabbit fetus, showing that predominantly feminine structures remain after castration of the male. (From Jost.[17])

procedures Jost opened the abdomen and uterus of pregnant rabbits, exposed the fetal gonadal areas, and excised them. If this was done at 20 days, the male fetuses developed intersexually. Figure 30 shows the normal female development on the left, the normal male course in the center, and, on the right, the intersexual structures resulting from the uninhibited progression of the basic female pattern. That the testis acts as an organizer was also shown by experiments in which a

fetal testis was placed alongside the fetal ovary. The müllerian development was inhibited and local wolffian structures became dominant.

The same phenomena may occur in the human fetus if the testes are not properly formed. Three main types may be recognized clinically: hypospadias, testicular feminization and gonadal dysgenesis.

Hypospadias

It is hard to prove that hypospadias (Fig. 31) results from inadequate testicular stimulation, but such a hypothesis conforms best with the

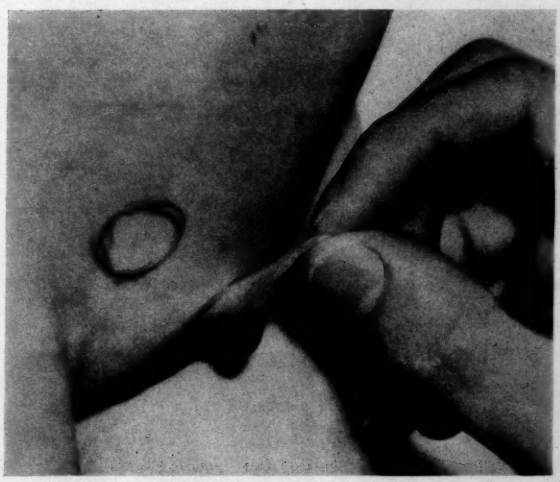


Fig. 31. External genitals in typical perineal hypospadias, showing intersexual phallus and cryptorchidism.

known facts. That hypospadias is a form of intersexuality was well shown at this Clinic by Howard,[13] who demonstrated the correlation between the size of the vagina and the degree of chordee and meatal displacement (Fig. 32). An extreme example is illustrated in Figure 33. The phallus looks like an enlarged clitoris and the urethra is in the normal female position, yet the sex chromatin was male in distribution; in spite of apparently normal female internal genitals, the gonads were testes, although somewhat deficient in Leydig cells.

Testicular Feminization

Gonads with the microscopic appearance of tubular adenomas have been found in the inguinal canals of patients who otherwise appear quite

feminine. Scant body hair and a rudimentary vagina are abnormalities which are often associated (Fig. 34, A). The development in these persons corresponds to that of Jost's rabbits, since their feminine development is uninhibited by true male gonads.

The correspondence is not complete, however, since müllerian development in the syndrome of testicular feminization is never beyond the merest rudiments. This is in contrast to the formation of uterus and tubes in Jost's experimental animals and in male and female patients

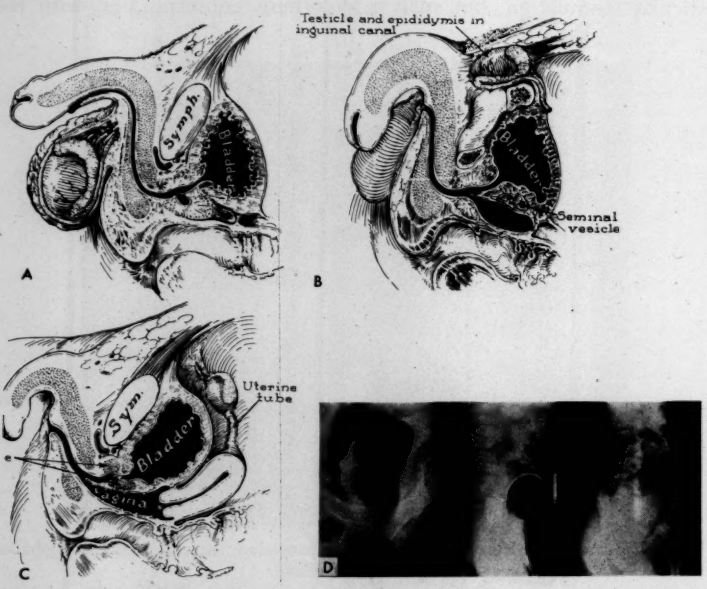


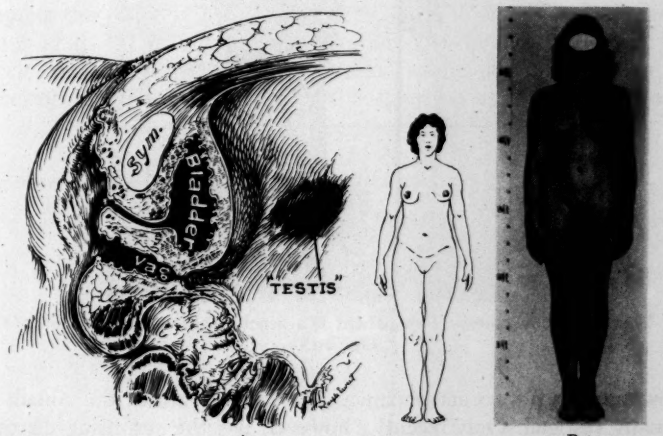
Fig. 32. A, First-degree hypospadias, with minimal enlargement of the prostatic utricle. B, Penoscrotal hypospadias, with definite enlargement of the prostatic utricle. C, Perineal hypospadias, with even more extreme feminization. D, Vaginograms with air cystograms of 3 children with hypospadias and enlargement of the prostatic utricle. (From Howard.[13])

with gonadal dysgenesis. Also, the "testes" secrete estrogen and androgen as does the normal ovary, so that intersexuality in these cases is not on a purely hormonal basis.

The similarity between persons (absence of pubic and axillary hair, inguinal hernia and gonadal dysgerminoma) with this syndrome suggests a genetic conditioning, and this is reinforced by the fact that there is a known familial incidence.

Figure 34, B, shows the patient who was described by Goldberg at this Clinic, thus crystallizing our understanding of the syndrome.[7] Such

Fig. 33. Intersexual genitals in male, showing extreme degree of hypospadias syndrome.



A B

Fig. 34. Testicular feminization. A, Diagram of usual internal genitals, adenoma tubulare group. Note the gonad resembling rudimentary testis; no epididymis; failure of muellerian duct development; normal female external genitals. *B*, Patient with typical feminine habitus. (From Goldberg.[6])

persons must be regarded as irreversibly female in spite of the male chromosomal pattern and gonads.

Gonadal Dysgenesis

Turner's syndrome (eunuchoidism, associated with web neck, increased carrying angle of the forearm and other anomalies) is well

Fig. 35. Gonadal dysgenesis. This patient is a genetic (chromosomal) male. (From Gordan.[8])

known, and is always accompanied by "streak ovaries"; the gonads are virtually vestigial. Only recently, however, has the surprising discovery been made that most of these patients, in spite of their feminine appearance, are actually chromosomal males (Fig. 35).

In *summary*, suppression of testicular function during fetal life allows the basic female pattern to develop unhindered. The result is male pseudohermaphroditism, which can range from minor degrees of hypospadias at one extreme to normal female appearance at the other.

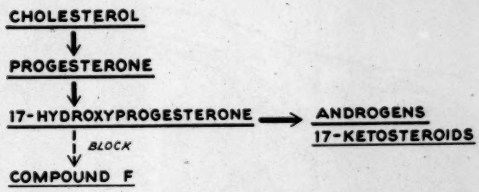


Fig. 36. Postulated diversion in cortisone metabolism with congenital adrenal hyperplasia. (After Bongiovanni,[2] Hechter et al.[9] and Jailer.[16])

MASCULINIZATION OF FEMALE

Burns[3] experimented on the fetus of the opossum; the animal is born early in fetal life and develops outside, clinging to the maternal nipples. Burns found that by rubbing the abdomen of the fetuses with testosterone, those destined to become female were masculinized, and developed a large phallus and intersexual internal genitalia.

Adrenal Hyperplasia

If, because of a congenital defect mediated through genetic influences, the metabolic pathway for the formation of adrenal corticoids is deranged (Fig. 36), excessive androgens are produced. These androgens do not suppress the pituitary gland, which continues to stimulate the adrenal cortex (Fig. 37). The result is masculinization of the fetus (Fig. 38), which continues after birth. In addition, some degree of adrenal insufficiency is common because of the diversion of the adrenal cortex

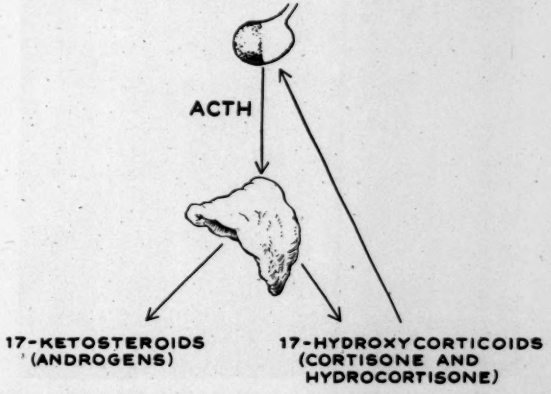


Fig. 37. Diagram showing that androgens do not inhibit the production of ACTH by the pituitary, but that corticoids (endogenous or administered) do.

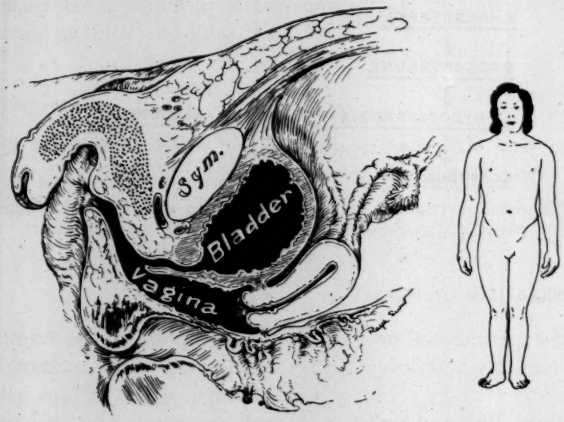


Fig. 38. Diagram of characteristics of female adrenal intersexuality, showing normal ovaries and derivatives of the muellerian ducts, but with masculinized urogenital sinus by androgenic hyperfunction of the adrenal cortex. (From Howard.[13])

from cortisone production. The fetus will be masculinized to a greater or less degree, depending on the age at which adrenal activity begins, and especially on the amount of androgen produced.

An example of fairly extreme alteration is seen in Figure 39. The urethra extends partway down the shaft of the enlarged phallus. The child died soon after birth from adrenal insufficiency. The changes were

Fig. 39. Infant with congenital adrenal hyperplasia. The clitoris is large, and a urethra runs well down the shaft. (From Reilly, Hinman et al.[21])

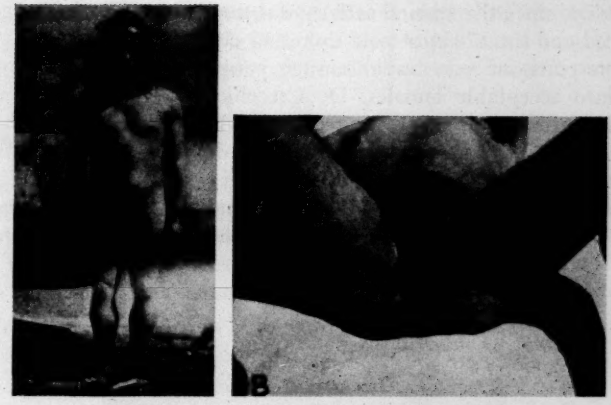


Fig. 40. Untreated case of congenital adrenal hyperplasia in the female, showing short stature and definite masculinization. (From Hinman.[12])

Fig. 41. Adrenal hyperplasia treated with estrogens (precortisone era). Note limited height, hirsutism, meager breast development.

progressive, since the adrenal activity was continuous. The bone age was advanced and the 17-ketosteroid excretion elevated.

Before cortisone was available, such patients were difficult to transform into acceptable females. De Crecchio's original patient[5] was a valet. His attempt to marry was blocked by the Church because he had been registered at birth as a girl. He then drank himself to death (although it took him 20 years to do it).

Figure 40 shows the result of withholding treatment from these patients. In spite of the administration of estrogens, depilation and cli-

Fig. 42. Partial reversal of progressive masculinization in case of congenital adrenal hyperplasia with cortisone therapy. (From Goldberg.[6])

toridectomy, such patients had difficulty adjusting as women (Fig. 41). We converted two girls who were masculinized from adrenal hyperplasia, into males by plastic repair of the external genitals[10]; the parents have been satisfied with the result. Now that cortisone is available, however, we feel that an alteration to maleness is not the appropriate treatment, since the person is sterile, short in stature, and pigmented, and often has other stigmata of adrenal insufficiency.

Cortisone, by suppressing ACTH production, re-establishes the balance between the pituitary and adrenal glands. Overproduction of

androgens stops, and exogenous cortisone replaces the diverted endogenous source. The result (Fig. 42) is a release of normal female characteristics; these patients develop normally, and even become pregnant.

Maternal Arrhenoblastoma

Several instances have been reported of the development of a functioning arrhenoblastoma during pregnancy. These maternal androgens affect the human fetus in the same way that the applied testosterone affects the young of the opossum (Fig. 43). The child, basically female, is born with a large phallus and other male characteristics. These changes are, of course, not progressive.

Fig. 43. Intersexual female infant born to a mother in whom a functional arrhenoblastoma developed during pregnancy. (From C. P. Brentnall.[3])

Administered Hormones

If enough testosterone were given the mother early in pregnancy, while sexual differentiation is taking place, masculinization of the female fetus would be possible. These changes have been recorded in animal experiments. Such an etiology was considered in one case we saw in consultation (Fig. 44). The mother of this child (which was

born with a large phallus and clitoral urethra) received enough androgens during the first trimester to cause hair growth and deepen the voice.

In *summary*, androgens, either from altered metabolic pathways in the fetal adrenal cortex or from maternal sources, cause masculinization of the developing female fetus. Secretion of the adrenal androgen continues after birth unless suppressed by exogenous cortisone.

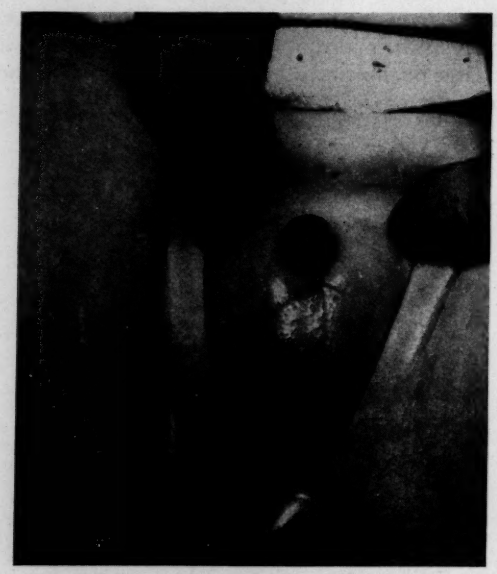


Fig. 44. Phallic urethra and other intersexual characteristics in a child whose mother received testosterone therapy during the first trimester of pregnancy. (From Bates and Grunwaldt.[1])

DIAGNOSTIC STEPS

Certain questions must be answered in each case to permit appropriate treatment.

First, what is the *chromosomal sex?** Barr[19] and his associates have given us an apparently reliable means of determining the child's

* *Chromosome Analysis.*

A. *Buccal smear* or *vaginal smear:* (1) Scrape buccal mucosa clear of mucus. With glass slide, scrape epithelium. Spread thickly on second slide, place at once in *Davidson's* solution. Stain with Papanicolaou or Fuelgen stain. Count chromatin spots. (2) 80 per cent or over is female; 20 per cent or less is male. If between, smears are not adequate for diagnosis.

B. Skin biopsy is similar to the above. Fix in Davidson's solution.

genetic sex. This does not, of course, necessarily solve the clinical problem, since we cannot force every intersexual child to conform to its genetic sex. It does allow classification, however, and hence permits a rational program based on predictable future developments.

Second, are there *excessive androgens?** The bone age will be advanced if androgen secretion continues after birth, the result, for example, of adrenal hyperplasia. The 17-ketosteroid excretion will be ele-

TABLE 8. *Differential Diagnosis in Intersexuality*

	ANOMALIES (BLIGHT)	MALE PSEUDOHERMAPHRODITE (SUPPRESSED TESTES)	FEMALE PSEUDOHERMAPHRODITE (EXCESS ANDROGEN)
Examination	Abnormal phallus Other anomalies: imperforate anus, duplication, urinary tract anomalies, other systems	Hypospadias to female external genitals Vaginal size proportional to degree of hypospadias Usually palpable prostate	Enlarged clitoris Urogenital sinus Often palpable uterus
Chromosome analysis	Either male or female	Male	Female
Hormone tests			
1. 17-KS	Normal	Normal	Elevated
2. FSH	Normal	Normal or high	Normal or low
Urethrocystograms and vaginograms	Bicornuate uterus Other anomalies	No uterus or cervix	Small uterus and cervix
Bone age	Normal	Normal or retarded	Advanced
Cortisone therapy	No effect	No effect	Reduce 17-KS Reverse
Surgical exploration	Gonads and internal genitals of either sex; other anomalies	Inadequately developed male gonads and internal genitals	Normal female gonads and internal genitals

* *Hormone Tests.*

A. *17-ketosteroids*

1. Elevated with adrenal hyperplasia (and decreased after cortisone therapy).

2. Collect 24-hour urine specimen with 15 cc. concentrated HCl as preservative. 17-ketosteroids are determined colorimetrically.

3. Normal levels: near 0 to age of 8, rising to 1.5–5.0 before puberty, then to adult levels of 15 (± 5) mg. per 24 hrs. in males and 10 (± 5) mg. in females. If the level is >2.5 soon after birth, this is diagnostic of adrenal overactivity.

4. The beta fraction will rise from normal levels of 5% of total neutral 17-ketosteroids to over 50% with adrenal hyperplasia.

B. *FSH (follicle-stimulating hormone)*

1. Elevated with gonadal deficiency; decreased in primary pituitary deficiency.

2. 24-hour urine specimen. This method uses immature mice.

3. The normal adult level is above 5 and below 50 mouse units per 24 hours. The test in children is less valuable than in adults, since low levels are normally encountered before puberty.

vated under the same circumstances. Cortisone, given as a diagnostic test, will reduce the excretion to normal if adrenal hyperplasia is its source.

Third, are there *other anomalies*? Anal, vesical or congenital defects of other organ systems (occasionally approaching monster formation) rule out endocrinologic causes for the intersexual genitals and establish blight as the etiologic factor.

Fourth, is the child so old that the *sexual orientation* of its personality is fixed, and could be reversed only with real psychic harm?[18] Only overwhelming anatomic reasons would lead one to change the designated sex of an older child by surgical procedures (Fig. 45).

	APPEARANCE	HORMONE	REARED AS	SEXUAL ORIENTATION
FEMALE PSEUDOHERMAPHRODITE:				
ADRENAL HYPERPLASIA	15 ♂	15 ♂	15 ♀	15 ♀
MALE PSEUDOHERMAPHRODITE:				
TESTICULAR FEMINIZATION	1 ♀	1 ♀	1 ♂	1 ♂
HYPOSPADIAS	2 ♀	2 JUV.	2 ♂	2 ♂
WITH CRYPTORCHIDISM	2 ♂	2 ♂	2 ♀	{1 ? ♂ 1 ♀
SAME, WITH MULLERIAN ORGANS	2 ♂	1 ♂ 1 JUV.	2 ♀	2 ♀

Fig. 45. Sexual orientation with nonconforming external genitals. (After Money, Hampson and Hampson.[18])

Fifth, can one be *positive of the diagnosis* on the basis of the various tests and examinations? If not, the surgeon should expose the internal genitals by laparotomy early in life so that a final decision can be reached. The child then can be irrevocably raised in this designated gender.

TREATMENT

The treatment of the young patient will depend on (1) the type of intersexuality and its etiology, and (2) the degree of deformity. Proper classification is important, since later development in a contrary direction might occur (as, for example, in a male pseudohermaphrodite, hypospadias type, if raised as a female). The degree of deformity will determine whether or not it is *possible* to reconstruct the genitals by operative procedures to fit the assigned sex.

Instructions are then given the parents to raise the child in the assigned sex. If doubt or confusion is absent, the child will develop emotionally in a normal manner.

TABLE 9. *Treatment of Intersexuality*

	TYPE	CAUSE?	PROCEDURE	FINAL SEX
Female pseudo-hermaphrodite	Adrenal	Androgen	Remove source	Female
	Anomaly	Blight	Varies	Male or female
Male pseudo-hermaphrodite	Hypospadias	↓Testis	Correct surgically	? Male
	Testicular feminization	↓Testis	? Vaginoplasty ? Gonadectomy	Female
	Gonadal dysgenesis	↓Testis	Hormonal	Female

SUMMARY

1. Intersexuality arises from (1) anomalous development in either sex (blighting), (2) ascendancy of the basic female pattern in the male (testicular inadequacy) or (3) masculinization of the female fetus (adrenal hyperactivity).

2. Although the child's sexual orientation will conform to the assigned sex, the child will adjust to the sex appropriate to the external genitals and to the hormonal changes which will occur with maturation.

3. An understanding of the etiology of the particular case of intersexuality allows application of appropriate surgical, hormonal and psychologic treatment. Determination of the chromosomal sex, identification of excessive excretion of androgens, examination for associated anomalies, assessment of sexual orientation of the personality, and perhaps gonadal biopsy are necessary.

4. It is preferable to adapt the external genitals to the true sex. If this cannot be done, then the sex must be changed to conform with the genitals.

EDITOR'S NOTE. Progesterone given for repeated abortion can bring about pseudohermaphroditism. W.A.R.

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DWARFISM

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DEFINITION; TERMINOLOGY

Dwarfism designates a considerable defect in growth (height). As in any abnormality based on quantity rather than on quality, an exact delineation is not possible, and arbitrary limits have to be established. Thus it has been suggested to designate adult persons as dwarfs if their height does not exceed 120 cm. (48 inches). By another, equally arbitrary definition, the term is applied to persons whose height is at least 30 per cent less than the mean normal of the respective population. Defining dwarfism with reference to the growth tendencies of a population takes the variation of the latter into account and could, at least theoretically, be applied to any age group rather than only to adults.

We have not restricted the present review to any arbitrary limits. Extreme cases of dwarfism are comparatively rare; in clinical practice we are more commonly confronted with the less extreme instances of growth deficiency.

FACTORS DETERMINING GROWTH

It is generally stated that growth is determined by three sets of factors: (*a*) genetic (hereditary), (*b*) nutritional, and (*c*) hormonal.

Genetic Factors

The role of genetic factors is evident from the tall and short lines obtained by selective breeding in different species. In man, studies on identical (homozygous) twins show height to be a highly correlated

quality. There is evidence that, at least in certain instances, the effects of genetic and perhaps nutritional factors are mediated by the endocrine system. An example of a genetic factor mediated by the anterior pituitary is the recessive hereditary dwarfism in a strain of mice.[36, 37] The genetic abnormality is that of a deficiency of eosinophilic (growth-hormone-producing) cells of the anterior pituitary; and growth can be induced in such dwarfed mice by administration of anterior pituitary material. It should, however, not be inferred that all hereditary differences of growth are necessarily the result of genetically determined differences of growth hormone production; this is possible, but there is, at present, no evidence for it.

Nutritional Factors

The possibility must be envisaged that nutritional factors, limiting growth, may operate through inhibiting the production and/or secretion of anterior pituitary hormones. This has been actually demonstrated for limited growth processes. Growth processes in the ovary and uterus incident to cyclic ovarian function cease in malnutrition, but can be induced by administration of gonadotropic hormones.[40] Whether we are entitled to extrapolate this to inhibition of over-all growth in the partially starved animal is a matter for speculation; there is at this time no conclusive evidence.

Regardless of the extent to which nutritional factors may influence growth by an influence upon endocrine glands, the fact is well established that quantitatively or qualitatively, inadequate alimentation prevents optimal growth. Stunting of growth in populations suffering from starvation in two world wars bears evidence to this fact. However, stunting of growth due to inadequate food intake does not usually reach the extremes of dwarfism; the disease conditions causing dwarfism through nutritional deficiencies will be discussed subsequently. On the other hand, it is generally assumed that the increased average height achieved in comparable samples of the population in England and in the United States over the past 30 years is due to improvement of nutrition.

Hormonal Regulation of Growth

The central role of growth hormone is amply established. Excess of this hormone causes gigantism, and the arrested growth of the hypophysectomized animal is resumed under treatment with growth hormone. The well known influence of thyroid hormone, evidenced by the growth arrest of the thyroidectomized young animal and by the human cretin, is possibly of an indirect nature. Thyroid hormone fails to induce

growth or nitrogen retention in the hypophysectomized rats, whereas growth hormone is effective in the thyroidectomized animal. Furthermore, thyroidectomy is followed by loss, and treatment with thyroid hormone by reappearance, of eosinophilic granulation in the anterior pituitary. Since the eosinophilic cells are the source of growth hormone, these latter findings, together with the results of injection experiments mentioned above, suggest that the influence of thyroid hormone upon growth may be to a large extent indirect, by way of influencing secretion of growth hormone.

Hormonal influences on growth are certainly not limited to these two hormones. A statement that optimal growth is predicated upon balanced, homeostatic secretion of all hormones will hardly be questioned, although the practical value of such insight, for clinical diagnostic purposes, may be limited. To exemplify this further, it should be remembered that the growth of adrenalectomized young rats is inhibited, growth being resumed by adequate replacement therapy; on the other hand, excess of 17-hydroxycorticosteroids (cortisone, hydrocortisone) causes stunting of growth due to their protein catabolic action.

The role of the sex steroids, though clinically evident, is not fully understood. Certainly, androgens of testicular or adrenal origin enhance protein anabolism and growth; children with adrenal or testicular lesions causing excess of androgen secretion are tall, but, as a consequence of early closure of the epiphyses, their ultimate height, if they are not treated, is subnormal. The "pubertal growth spurt" of normal children is probably due to the secretion of testicular and adrenal androgens; whether, in girls, the estrogen secretion from the ovary, or the concomitant androgen secretion from the adrenal cortex (adrenarche of Albright) is decisive is not certain, but the latter is more probable.

On the other hand, the prepuberal castrate usually continues to grow continuously without the puberal "spurt" up to an age of 20 and beyond, achieving an excessive height. It has been suggested that normally the sex steroids inhibit growth hormone secretion, and that the latter continues in the prepuberal castrate.

In view of the absence of an adequate assay procedure for growth hormone in body fluids, evidence for this hypothesis is circumstantial only. It is possible that the decisive factor in the prepuberal castrate is the absence of timely closure of the epiphyses, without an actual change in secretion levels of growth hormone.

TRUE (PRIMORDIAL) DWARFISM (NANOSOMIA VERA)

These dwarfs represent the "miniature edition" of human species. Reportedly, these persons are diminutive at birth; their percentage increment is normal; they go through a normal puberty and timely

epiphysial closure. The body proportions of these midgets are those of normal adults. The latter point has been questioned; some of the miniature individuals are not perfectly proportioned (Günther), although they otherwise conform with the picture outlined above.[20]

Probably some of the historically renowned dwarfs, attendants of royalty and nobility of former times, belong in this group (Boruwlaski, Charles Strafford, presented by Phineas T. Barnum as General Tom Thumb, and others[41]). Other court dwarfs were achondroplastic dwarfs or hunchbacked rachitic dwarfs, which will be discussed below.

According to historical records, a number of these dwarfs were fertile; they married and procreated children.[41] Their normal, though diminutive, appearance and their intelligence are attested to; a portrait of Boruwlaski is reproduced in Thompson's monograph.[41] Analyses of family histories have indicated that this mutant is, in most cases, a simple recessive trait.[18] It is believed that this hereditary, recessive mutant gives rise to the occurrence of pygmy races or tribes through selective breeding. Such pygmies have been observed in several parts of Africa, and are sometimes referred to as Negrillos. In southern Asia common characteristics of widely scattered pygmy races are noted; a common origin has been suggested hypothetically, and all these Asian pygmies are sometimes called Negritos.

There is, at present, no evidence that true, primordial dwarfism is caused by a lack of growth hormone, although, on the other hand, the hypothesis that the "dwarfing gene" causes an isolated growth hormone deficiency cannot be ruled out at this time.

For heuristic purposes, we wish to consider the pituitary dwarf (infantilistic, type II ateleiotic dwarfs) as a pathogenetically separate entity (see below). Note, however, that there is at this time no conclusive proof, and only circumstantial evidence, that the two conditions are qualitatively different, and not merely different degrees of a pituitary disturbance.

ENDOCRINE DISORDERS

PITUITARY DWARFISM

Pituitary Dwarfism Resulting from Organic Lesions of the Pituitary; Dwarfism as a Feature of Panhypopituitarism

As would be expected, a lesion destroying the anterior pituitary causes cessation of growth; if this occurs early in life, the stature will be that of a dwarf. Such destruction of the pituitary is not selective, however, and one will find evidence of associated deficiency of hormones other than that of growth hormone. At the age of puberty secondary sex characteristics fail to develop, and in girls menses do not appear. Deficiencies of thyrotropic and adrenocorticotropic hormones may not be

apparent in the clinical picture, but can often be detected by appropriate tests of thyroid and adrenocortical function. Few cases of this type have been completely studied with the use of currently available methods; extrapolating from studies of pituitary tumors in adults, one may expect to see a considerable variation, with some degree of thyrotropic and adrenocorticotropic functions continuing for some time.

The most common lesion in childhood is the *craniopharyngioma*; chromophobe tumors, which top the list in adults, are exceedingly rare in prepuberal persons. The neurological signs associated with craniopharyngioma are well known, but it is not generally appreciated that growth failure almost always antedates the appearance of neurological signs and symptoms and is usually the first sign. Arrest or retardation of growth may precede neurological manifestations by as long as 10 years.[24] Roentgenograms of the skull should therefore be obtained in children with growth arrest of obscure origin. In rare instances, tuberculosis and syphilis, as well as xanthomatous lesions (Hand-Schueller-Christian disease),[1] are the cause of pituitary destruction. In a case observed by the authors toxoplasmosis was associated with stunting of growth and hypogonadism. Lesions were demonstrable roentgenologically in the brain, and were assumed to be located also in the anterior pituitary.[45]

Pituitary Dwarfism without Demonstrable Lesion of the Pituitary

There is an abundance of cases reported as pituitary dwarfs, presenting a rather typical clinical picture. These appear of normal size at birth, and their development and gain in height and weight remain normal for a few years. Then, usually between the ages of one and three years, the growth curve flattens, either with complete arrest or more often with continued, small increments. Body proportions do not change as they normally do with progressing age and height. Epiphysial development is retarded. There is no clinical evidence of hypothyroidism. On roentgenegrams the sella turcica appears normal. Small size of the sella is mentioned in some reports, but the size is evidently in proportion to the small size of all structures. Bridging of the sella was at one time considered significant, but is now generally recognized as a normal variant. Mental development is usually normal. Emotionally and socially, there can be serious difficulties, as would be expected, as a result of awareness of a progressively increasing difference from the age and playmates. When these children reach puberal age, they fail to show any puberal development; for this reason these cases are sometimes referred to as infantilistic dwarfism. The epiphysial lines remain open, sometimes up to the third or fourth decade of life, and slow but progressive growth up to this time has been recorded. This fact is known and dreaded by circus midgets, who, while still remaining dwarfed, may

just outgrow the lilliputian height at which they are considered attractive, and thus lose their livelihood.

In the old descriptive nomenclature these dwarfs were, together with the primordial, true dwarfs, called proportional dwarfs, in contradistinction to the grossly disproportional dwarfing in achondroplasia, rickets, and the like. The body proportions of these dwarfs remain infantile, however, in contradistinction to those of the primordial dwarf.

These cases are reported as pituitary dwarfs under the assumption that the condition is caused by absent or inadequate secretion of growth hormone, and later by that of gonadotropic hormones, whereas a normal secretion of thyrotropic and adrenocorticotropic hormone is assumed because of absence of clinical signs of hypothyroidism and hypoadrenocorticalism. The designation of Lorain-Levy type is sometimes used for these cases, although the resemblance between the case reported by Levy and the cases now designated by his name is somewhat superficial.

The evidence that persons presenting the picture outlined above actually suffer from a (partial) anterior pituitary insufficiency is only inferential and indirect. The fact that the clinical picture is practically identical with that resulting from lesions involving the pituitary (especially and most commonly craniopharyngiomas; see above) can be quoted in favor of the assumption of hypopituitarism in these cases. With regard to the hypogonadal, "infantilistic" facet, we are on safer ground. In a hypogonadal person who has never undergone puberal development the absence of gonadotropic hormone in the urine clearly indicates pituitary failure in contradistinction to a primary gonadal failure. The importance of this test in differentiating pituitary dwarfism from gonadal dysgenesis associated with shortness of stature will be emphasized in the discussion of the latter condition.

Can the lack of growth hormone, inferred from the clinical picture, be substantiated by metabolic studies? Most cases were reported at a time when neither knowledge regarding metabolic actions of hormones nor techniques for their study were available. In view of the present knowledge of the role of growth hormone in carbohydrate metabolism, the question may be asked whether these dwarfs should exhibit an abnormal sensitivity to insulin (hypoglycemia irresponsiveness). Since both adrenocortical hormones and growth hormone are believed to have an "anti-insulin" action, there is at this time no unequivocal experimental evidence as to what the response to insulin "should" be in a case of growth hormone deficiency with intact pituitary-adrenocortical axis. Hypoglycemic episodes have been observed in a dwarf presumably belonging in this category,[39] and increased insulin sensitivity (hypoglycemia irresponsiveness) has been reported,[34] but a greater number of such studies will have to be available before the value of such a test for the diagnosis can be analyzed. The protein anabolic action is one of

the essential actions of growth hormones, as evidenced from experiments on animals, hypophysectomized or intact, treated with growth hormone. It would be expected that the hypopituitary nature of the dwarfism under discussion could be substantiated by nitrogen balance studies. Few such studies have been reported; it is disturbing that Wang et al., in a balance study of a 10-year-old dwarfed boy, diagnosed as of the Lorain-Levy type, found the protein metabolism typical of a rapidly growing child;[43] but there is a strong suggestion that this boy was not a "Lorain type" dwarf, because he showed a height increment of 2.1 cm. during the 51 days of study in the metabolism ward, but failed to exhibit any further growth during the next nine months in his home environment. It is probable that the dwarfing in this case was due to malnutrition rather than to hypopituitarism. In another extensive metabolic study, some subjects probably were pituitary dwarfs; they showed a positive nitrogen balance.[34]

Hypopituitary dwarfism of this type cannot be reproduced in the experimental animal; but there is a form of dwarfism in mice which bears some resemblance to the clinical picture under discussion. In the dwarf Silver mouse dwarfing is transmitted by a recessive gene. The pituitary gland of the dwarfs shows absence of eosinophilic cells, indicating the lack of growth hormone production. Administration of anterior pituitary suspension induces growth and gonadal maturation.[36, 37]

The thyroid gland and the adrenal cortices are defective. The testes show spermatogenesis and mature sperm even though they are not as numerous as in normal controls. As judged from the size of the seminal vesicles, Leydig cell function of the testes appears adequate. The ovaries of the dwarfs are immature; follicles with cavities are rare, and the uterus is infantile; opening of the vaginal orifice rarely occurs. However, it has been stressed that the degree of immaturity of the ovary is not as extreme as in prepuberally hypophysectomized rats.

By comparing the dwarf Silver mouse with hypopituitary dwarfs in man, certain similarities are striking. Both the dwarf Silver mouse and the human hypopituitary dwarf are not dwarfed at birth, but grow for some time. The "sexual infantilism" of the female dwarf mouse may be similar to that of most human dwarfs of this type, but in exceptional cases ovarian function is fairly normal, as, for example, in a dwarfed woman reported by Hewer.[21] The fairly good testicular function of the dwarfed mouse, however, contrasts with the sexual infantilism of almost all male hypopituitary dwarfs; exceptions, again, have been recorded: Schwarzer, for example, records a boy with hypopituitarism due to craniopharyngioma with good gonadal function.[33] As for thyroid and adrenal function and structure, there is evidence of disturbance in the dwarfed mouse; few studies have been reported in human hypopituitary dwarfs without organic lesion of the pituitary. On the basis of mental development and clinical appearance, it is usually stated that thyroid function is not deficient, and certainly these dwarfs are not cretinoid. Studies with currently available methods (protein-bound iodine [PBI], I^{131} uptake, conversion ratio, and so on) have been reported only in

a few cases; in one case, thyroid function is recorded as decreased, but the figures for PBI, I^{131} uptake and urinary excretion, and the serum alkaline phosphatase values appear borderline and not indicative of a significant degree of hypothyroidism.[34]

Similarly, not enough data on adrenocortical function are available; the few reported do not suggest hypoadrenocorticalism,[34] in contradistinction to those cases due to pituitary or parapituitary tumors, in which secondary adrenocortical insufficiency is frequently present.

It would therefore appear that the hypopituitarism of these dwarfs is probably limited to deficiency of growth hormone and of gonadotropic hormones. As mentioned above, evidence for the growth hormone deficiency is indirect and circumstantial only, since there is no adequate assay method sufficiently sensitive to demonstrate diminished or absent levels. The suggestive evidence includes diminished growth in the absence of other factors responsible for dwarfing, retarded epiphysial maturation and delay of closure of epiphysial lines, and sometimes retarded dentition. In a few instances increased insulin sensitivity has been observed.[34] This could be attributed to growth hormone deficiency only if the pituitary-adrenal axis were found to function normally. The dwarf Silver mouse shows increased insulin sensitivity, but in this animal there is morphological evidence of adrenocortical involvement;[29] the insulin sensitivity can, however, be restored in these mice with either cortisone or growth hormone.[29]

In man, paucity or absence of eosinophilic cells in the pituitary of such dwarfs has been reported, but the older investigators limited their observations to more or less routine examination of microscopic slides.[26] In a more recent case differential counts of the pituitary cells (based on the standard counts of Rasmussen) have shown a small number of eosinophils; in addition, the latter showed pyknosis and other signs of abnormality. This hypopituitary dwarf would compare well with the dwarf Silver mouse; however, this woman differed from most hypopituitary dwarfs, in man as well as in the dwarf Silver mouse, for there was no hypogonadism, and the dwarfed woman had actually given birth to a child.[21]

Diagnosis. The appearance of these dwarfs is so characteristic that the diagnosis should not be difficult in persons past the age of puberty. Other causes for dwarfing, which might result in an almost identical clinical picture ("pseudohypopituitary dwarfism"; see below), have to be ruled out. Difficulties could arise in the exceptional case in which gonadal function is normal (e.g., Hewer's case); in such a case the delayed osseous development, as well as the history of initially normal growth, would help to differentiate the case from one of primordial dwarfism. A finding of increased insulin sensitivity would probably support the diagnosis of hypopituitary dwarfism, but a normal response to insulin would, on the basis of present information, not rule it out.

In a case of "infantilistic," i.e., hypogonadal dwarfism, consideration has to be given not only to the group of "pseudohypopituitary dwarfs" (nutritional, hepatic, renal, cardiac dwarfs), but also the impaired growth in cases of gonadal dysgenesis. These persons are rarely severely dwarfed; in addition, the high levels of gonadotropic excretion, as well as the male sex chromatin present in about 95 per cent of the cases, help to differentiate the two conditions.

In the prepuberal child it is much more difficult to arrive at a definitive diagnosis. The latter will be suggested if, after two or three years of normal growth and development, the growth curve flattens out and epiphysial development is appreciably retarded, provided, of course, all other causes for such occurrence can be excluded.

TREATMENT. In cases of pituitary dwarfism due to craniopharyngioma, treatment of the latter of course takes precedence. Results of surgical treatment have not been very satisfactory, and up to recently craniopharyngiomas were considered resistant to radiation. Recently, promising results were obtained by aspirating the cystic part of the tumor, followed by radiation with high doses.[25] After successful treatment of the tumor, treatment of the growth and gonadal deficiency will be necessary if the pituitary, in spite of relieved pressure, fails to resume adequate function. Treatment at this stage does not differ from that of nontumorous cases ("Lorain-Levy" type).

Attempts to induce growth with growth hormone preparation have been almost uniformly unsuccessful. Even highly purified and highly potent preparations of beef growth hormone are almost always totally inactive in man. This is due to a unique species specificity of growth hormone; whereas growth hormone prepared from beef pituitaries fails to induce growth or nitrogen retention in man and monkeys, growth hormone prepared from monkey and human pituitaries is effective in man. This is evidently due to the different structure and amino acid composition of the growth hormone polypeptide, which is similar in monkey and human growth hormone, but different in the hormone of bovine origin.[27] Since monkey and human growth hormone preparations are not available, and probably will not be available in adequate quantities, treatment with this hormone is impractical. It has been suggested that it might become possible to prepare an "active core" from beef growth hormone which would be similar to that of human growth hormone. If this feat of protein chemistry is achieved, therapeutic use of growth hormone may become possible.

Attempts have been made for a long time to utilize the protein anabolic action of testosterone for induction of growth. There is little question that treatment with androgens increases the growth rate; in the typical growth curve this is evidenced by a steeper slope of the curve during androgen therapy as compared with the slope of the growth curve

before institution of active therapy. This may be of considerable importance from a psychological standpoint, and may improve outlook and social adjustment greatly at a time when the youngster is becoming increasingly and painfully aware of his otherness. However, the ultimate height attained is almost always subnormal. This is tentatively ascribed to an early closure of epiphysial lines precluding further growth.

It has been shown that, with the use of methyltestosterone, bone age usually advances more rapidly than height age, and that increased rate of epiphysial maturation continues for some time after hormonal therapy has been discontinued. In no case of this series was treatment actually continued to the point of precocious closure of the epiphyses. The latter was predicted by extrapolating the curve of epiphysial maturation seen during the period of treatment, and by analogy with the child with precocious puberty or with adrenocortical hyperplasia. Unfortunately, the data in this series do not indicate whether during the treatment period height age or bone age was brought up to normality, or exceeded the latter.[38]

Clearly, more research on these aspects is needed. In the past several years considerable effort has been directed toward developing synthetic androgen derivatives with a higher ratio of protein anabolic:androgenic effect, as compared with that of testosterone. It will have to be seen whether the effect of an androgen on epiphysial maturation and/or on epiphysial closure is more closely related to the androgenic or to the protein anabolic action of a compound.

We do not advocate the indiscriminate use of testosterone in the somewhat slowly growing child, but would limit this therapy to severely stunted persons.

DWARFISM DUE TO HYPOTHYROIDISM

It is well known that the cretin is dwarfed; this is true of any form of cretinism, including the endemic cretin in certain goiter belts, the cretin due to congenital thyroid aplasia and the usually goiterous cretin with an inborn deficiency of synthesis of active hormonal compounds. As was discussed above (p. 926), it is probable that the dwarfism of cretins is due in part to a lack of growth hormone production; the latter is probably dependent on the presence of thyroid hormones. Over and above this indirect effect of thyroid hormone on growth, thyroid hormone appears to synergize the effect of growth hormone. This is evident from the increased growth obtained in the hypophysectomized rat by simultaneous administration of growth and thyroid hormones, as compared with the effect of growth hormone administration alone.

In the untreated thyroaplastic cretin, growth is not completely absent. For instance, an untreated cretin, age 11 years, observed by us had a

height age of two years. Whether this is due to the fact that in many instances the thyroid aplasia is not complete, and minimal but varying amounts of thyroid tissue are present, cannot be stated with certainty.

The growth retardation of the cretin is associated with greatly retarded epiphysial development, resulting in a definite retardation of "bone age." Furthermore, the epiphysial nuclei which do appear, though belatedly, in the untreated cretin frequently show epiphysial dysgenesis, giving a stippled appearance in the roentgenogram. The statment that the presence of a normal epiphysial development (normal bone age) rules out the diagnosis of severe hypothyroidism is generally valid, but curious exceptions occur; the authors have studied a five months old cretin with all clinical manifestations of the disease, and with an I^{131} uptake of 4 per cent and a PBI of 1.9 micrograms per 100 ml., but with a normal bone age. This could have been due to a "latent period" of somewhat greater length than is usually observed. Of course treatment was started immediately, and we can assume that, without treatment, a lag in epiphysial development would have become manifest at a later date. Other manifestations of thyroid deficiency are also present in cretins, including low or almost absent PBI and minimal uptake of I^{131}. The alkaline phosphatase in the serum is low, and this is believed to be the result of low osteoblastic activity. High serum cholesterol values are usually found in the older child, but rarely before the age of two years. The characteristic clinical picture includes mental retardation, delayed dentition, persistence of infantile body proportions, umbilical hernia, abnormalities of skin and hair, and others.

A more baffling picture is presented by the hypothyroid or cretinous child in whom hypothyroidism is the result not of absence of thyroid tissue, but of an inborn error of hormone synthesis. These children are almost always goitrous. The I^{131} uptake is high, and the PBI levels may be low, normal or slightly elevated. Detailed discussion of the different types of derangement of hormone synthesis are beyond the scope of this review. Chromatographic studies of the iodinated compounds of the serum, as well as comparison of protein-bound and butanol-extractable iodine, are necessary to unravel these cases.

Diagnosis of the typical cases is usually easy. The well known clinical picture is typical enough to suggest the diagnosis, which is confirmed by studies of parameters of thyroid function. The diagnostic problems of abnormal hormone synthesis are considered in the clinic by Reilly on Goitrous Hypothyroidism (p. 849). Commonly the question arises whether, in a child, retarded growth and a bone age lower than the chronologic age are due to hypothyroidism; the suspicion may be even greater if the child is mentally retarded. Such children should not be treated with thyroid hormone unless complete studies actually indicate the presence of hypothyroidism. We have entertained the idea that

perhaps in some such cases growth might be stimulated by an excess of thyroid hormone in spite of endogenous hormone levels adequate for maintaining a euthyroid state. Consequently, we have treated several euthyroid children of this type with desiccated thyroid; in no case have we obtained an increased growth or increased epiphysial maturation over and above the rates present before treatment. It is obvious that long-term observation before treatment is necessary for evaluation of possible effects.

GONADAL DYSGENESIS (OVARIAN AGENESIS, TURNER'S SYNDROME)

In almost all cases of gonadal dysgenesis there is definite stunting of growth, even though the height usually attained is above that arbitrarily set for the designation of dwarfism.

On the basis of sex chromatin studies, it has become clear that 95 to 98 per cent of these patients are genetically males. A detailed discussion of gonadal dysgenesis is beyond the scope of this review. The stunting of growth is evidently not a direct consequence of the absence of the gonads; in analogy with the prepuberal castrate, or the eunuchoid, one would expect excessive height. We rather have to regard the shortness of stature typically seen in those persons as yet another congenital anomaly, one of the many commonly found in association with gonadal dysgenesis. Epiphysial development ("bone age") is usually, but not always, lagging moderately. Whether the congenital anomaly responsible for stunted growth involves a lack of growth hormone secretion by the anterior pituitary (eosinophilic cells) is unknown. The fact that, in the pituitary dwarf, epiphysial lines remain open and growth continues up to the third or fourth decade of life, whereas epiphysial closure is usually only moderately delayed, if at all, in gonadal dysgenesis (and this in the absence of gonadal secretion!), makes the presence of a pituitary involvement less likely. The osteoporosis frequently seen in cases of gonadal dysgenesis is probably due to the lack of sex hormone secretion and is analogous to the osteoporosis found in castrates and eunuchoids.

Gonadal dysgenesis has, in most instances, been diagnosed only in puberal and postpuberal ages. Differentiation from hypopituitarism and pituitary dwarfism was based on the finding of castrate levels of urinary gonadotropins, and more recently on that of a male chromatin pattern in the majority of cases.

It is now becoming possible to establish the *diagnosis* in childhood and even in early infancy. Up to now this has been reported only rarely;[35] the authors have studied 10 cases of this disorder in prepuberal children. The suspicion will be aroused by the presence of various congenital anomalies, especially including webbing of the neck and con-

genital heart disease, in conjunction with poor growth; the presence of a male chromatin pattern will substantiate the diagnosis, but a female pattern does not rule it out. In several cases relatively high urinary gonadotropin levels (at an age when there is none normally) have been observed in infants and young children. In addition to the diagnostic value of this observation, it is of considerable physiologic interest inasmuch as it indicates that the anterior pituitary is capable of secreting gonadotropins long before the physiologic normal time of secretion, and suggests that the infantile gonad is not completely inactive, but normally secretes small amounts of an agent (presumably gonadal steroids) which prevent premature gonadatropin release.

PHEOCHROMOCYTOMA

Pheochromocytoma in children is occasionally associated with striking failure of growth;[10] the diagnosis will be made on the basis of other symptoms; especially, in a child, hypertension in the absence of the more common causes (kidney disease, coarctation of the aorta) should make one suspect pheochromocytoma.

PSEUDOHYPOPARATHYROIDISM

In 1942 Albright and associates described three patients in whom tetany was associated with hypocalcemia and hyperphosphatemia. These patients were distinguished from those with true hypoparathyroidism by failure to respond to parathyroid extract, with the usual increased urinary excretion of phosphate and rise in serum calcium. Other features which distinguished these patients from those with true hypoparathyroidism were the presence of ectopic calcification and ossification, dyschondroplasia manifested by short metacarpal and metatarsal bones, a characteristic short, round body and a round face. At least 31 instances of this syndrome have been reported, and it is now apparent that it is a genetic disorder. Elrick and colleagues[14] have suggested that three genes are involved—one causing insensitivity at the end organ to parathyroid hormone action, one leading to dyschondroplasia, and one inducing ectopic calcification and/or ossification.

In the majority of reported cases the presenting *symptoms* were those of tetany. In many instances an erroneous diagnosis of epilepsy was made because of the occurrence of generalized seizures, and the patient was treated with anticonvulsive drugs without amelioration of the seizures. A number of the patients had been treated with "gland injections" or thyroid hormone.[9] The short stature, round face, mental retardation and apathy seen in many of these patients may erroneously suggest the diagnosis of hypothyroidism.

Unfortunately, in many reports it is only stated that the patient was short, without giving any body measurements. When measurements are given, it is apparent that severe growth failure with permanent stunting may be associated with this disorder.[2, 22, 28] The majority of adults are over 4 but under 5 feet in height. The cause of the growth failure is probably related to the dyschondroplasia. The hypocalcemia probably does not contribute to growth failure, since patients with true hypoparathyroidism usually grow normally. It is more difficult to evaluate the role that the brain damage consequent to the frequent seizures and to intracranial calcifications may play in the growth failure. Another group of patients with the dyschondroplasia and ectopic calcifications, but without the chemical abnormalities of tetany, has been described and called pseudo-pseudohypoparathyroidism. The four reported instances of this syndrome in adults have all been short, varying in height between 55 and 62 inches.

It is apparent that pseudohypoparathyroidism should be thought of in children with growth failure. An early diagnosis and institution of proper therapy may prevent some of the deterioration of cerebral function that is a frequent consequence of untreated and protracted hypocalcemia.

CONN'S SYNDROME (PRIMARY ALDOSTERONISM)

In 1955 Conn[6] described a syndrome manifesting polyuria, polydipsia, hypertension, intermittent paralysis and tetany. Levels of serum sodium are elevated, serum potassium levels are low, and there is a metabolic alkalosis. Renal concentrating ability is severely impaired, although other tests of renal function yield normal results. The syndrome is caused by excessive production of aldosterone. Most cases have had adenomas or carcinomas of the adrenal cortex.

The only reported case of a child suffering from this condition has shown adrenocortical hyperplasia.[42] This patient had symptoms of polyuria and polydipsia from early childhood and probably had excessive production of aldosterone for many years. At 17 years of age he was small for his age (5 feet 3 inches), had a bone age of 13 years and was sexually immature. Van Buchem[42] has suggested that the retarded growth and development are caused by the potassium deficiency, which is an important part of this syndrome. However, we must await reports of additional cases in children before we can be sure that growth failure is a typical finding in this disorder.

RENAL DISORDERS

Although chronic renal disease is one of the more common causes of growth retardation, it is easily and frequently overlooked, especially in

infancy, until the kidneys are irreversibly damaged. When the renal disease has advanced and is complicated by osseous changes, it usually results in severe dwarfism. Renal disease may, however, be the cause of growth failure in the absence of osseous changes. West and Smith[44] have attempted to determine a common denominator for the growth failure associated with renal disease by an analysis of 41 children with chronic renal disorders. The manifestations that were studied for their possible effect on growth were (1) reduction of concentrating ability of the kidney, (2) chronic acidosis, (3) failure of excretion of metabolites as manifested by persistent elevation of serum nonprotein nitrogen or urea nitrogen levels, (4) inadequate caloric intake, (5) chronic infection of the urinary tract, (6) albuminuria. These authors found no evidence that mild azotemia, albuminuria or chronic urinary tract infection significantly affected growth. Although failure of renal concentrating ability was present in all instances with growth failure, it was also observed in a few children growing normally. The growth retardation of nearly all the patients in their series could be accounted for by the two factors of low caloric intake and chronic acidosis.

A urinalysis should always be performed in children with growth failure. The presence of alkaline urine, or of a low specific gravity, calls for further investigation even in the absence of other abnormal urinary findings. The blood urea nitrogen as well as levels of serum electrolytes should be determined, since acidosis and other disturbances of electrolyte metabolism are associated with renal disease. Levels of serum calcium and phosphorus may be necessary to recognize renal disease secondary to primary hyperparathyroidism or to idiopathic hypercalcemia of infancy. In order to rule out surgically correctible anatomic lesions, excretory urograms, cystograms and retrograde urograms may be necessary.

CENTRAL NERVOUS SYSTEM DISORDERS

The central nervous system must always be carefully investigated in instances of growth failure. A complete neurological examination, which includes a developmental appraisal and examination of the eye grounds and peripheral visual fields, is usually sufficient to determine the presence of organic disorders. The authors have seen a 19-year-old male with growth failure and delayed puberty who proved to have *toxoplasmosis* of the central nervous system. Detection of chorioretinitis on funduscopic examination would have been the important clue even in the absence of roentgenograms of the skull. Although this case has been classified as an instance of pituitary dwarfism[45] (see p. 929), it demonstrates the importance of examination of the central nervous system. *Craniopharyngiomas* are almost always associated with growth failure

as a result of encroachment upon the pituitary gland and/or on the hypothalamus. This is discussed in the section on Pituitary Dwarfism.

Familial dysautonomia is another disorder of the central nervous system which is associated with retarded physical growth and delayed osseous maturation.[30] Many of the patients with this disorder are frankly dwarfed and appear malnourished. Data on long-term follow-up of these patients sufficient to permit definitive statements are not available, but it appears that adult height may be below the mean, and puberal changes may be delayed in at least some instances. The pathogenesis of growth failure in this disorder is not known; Riley[30] suggested that it may in some way be related to the diffuse central nervous system disease. The other manifestations of this disorder should suggest the diagnosis. Some of the more common clinical features are diminished lacrimation, excessive perspiration, skin blotching, episodes of high fever, often without apparent explanation, and lability of blood pressure. Transient hypertension in older children has been severe enough to suggest a diagnosis of pheochromocytoma, and exploration for an adrenal tumor has been performed in five of these children. Postural hypotension is a constant finding. Other features include poor motor coordination, relative insensitivity to pain, hypoactive deep tendon reflexes, and emotional instability associated with attacks of severe vomiting. This condition is a congenital disorder frequently seen in siblings and is thought to represent the action of a simple autosomal recessive gene. The majority of cases have been reported in children of Jewish extraction.

SKELETAL DISORDERS

Deficiency of growth is associated with a wide variety of skeletal defects. The features of the true achondroplastic dwarf are too well known to warrant more than passing mention, but some of the less common varieties of chondrodystrophy are discussed in more detail.

ELLIS-VAN CREVELD SYNDROME

Chondroectodermal dysplasia (Ellis-Van Creveld syndrome) is a congenital abnormality with distinctive features differentiating it from other types of dwarfism. It consists in hypoplasia of teeth and nails, a rudimentary sixth digit, sixth metacarpal bones fused with the fifth metacarpals, and dwarfism. The dwarfism is due almost exclusively to shortening of the legs. Caffey has pointed out that the distalward progressive intensity of the shortening of the bones of arms and legs, as well as osseous changes, is characteristic of this syndrome.[4]

GARGOYLISM

Gargoylism (Hurler's syndrome) is a syndrome of unknown etiology. In the complete form the diagnosis can be made at a glance, but in the incomplete form, or in early stages of the disorder, only a high degree of suspicion and careful search can lead to the correct diagnosis. The distinctive clinical features include a dull coarse facies, hepatosplenomegaly, clouding of the corneas, semiflexion and limitation of motion of fingers, knees, and other joints. Pathognomonic skeletal changes are disclosed on roentgenograms. The osseous changes may be detected even in the absence of many of the characteristic clinical features.

CONGENITAL STIPPLED EPIPHYSES

Congenital stippled epiphyses is a rare disorder characterized by multiple, discrete, dense calcifications in many cartilaginous epiphyses demonstrable in the roentgenogram. Commonly, associated defects are present, including bilateral congenital cataracts, calcification of the trachea and larynx, flexion contractures, clubfoot, dislocated hips and cardiac defects. On physical examination the most characteristic abnormality is shortening of the extremities, most marked in the distal segments. This results in dwarfing of a type not unlike that seen in typical achondroplasia. In a few instances the occurrence of stippled epiphyses without shortening of the extremities has been reported.[3] There are no characteristic biochemical abnormalities, and the etiology is unknown. This disorder frequently terminates fatally before the first year of life, although the diagnosis has occasionally been first established as late as the third year of life.[16] If the patient survives the infantile period, the calcific lesions tend to disappear, and the child may be left with only slight stunting of growth.

MULTIPLE EPIPHYSIAL DYSPLASIA

Multiple epiphysial dysplasia is another developmental clinical entity, characterized by generalized irregularity in form and structure of the developing epiphyses. The disorder is bilateral and symmetrical, and the epiphyses usually appear two or three years late. The epiphysial centers tend to develop from multiple centers of ossification, giving a somewhat stippled appearance. The epiphyses finally tend to consolidate, and there is progressive improvement after puberty. These patients have few symptoms, but tend to be short and achieve an eventual height of about 5 feet.[23]

This disorder should not be confused with the epiphysial dysgenesis seen in cretinism (p. 935), since this condition requires no endocrine

therapy. Morquio's disease, gargoylism, osteochondritis and other osteochondrodystrophies should be differentiated from this disorder, since the prognosis differs considerably.

NUTRITIONAL DISORDERS

In many of the disorders discussed in this paper, including renal disease, inborn errors of metabolism, congenital heart disease, and others, the stunting of growth may in part be due to inadequate nutrition. More specific types of nutritional disorders causing dwarfism are those associated with defective absorption of necessary nutrients, such as is seen in fibrocystic disease of the pancreas and celiac disease. However, in *fibrocystic disease of the pancreas* it is difficult to assess the role that infection plays in contributing to growth failure. In *celiac disease* the defective growth may be sufficiently severe to result in permanent stunting.

It has been assumed that this defect in growth is a consequence of faulty absorption. Frazer[17] has recently suggested that the growth defect may represent an independent effect of inadequately metabolized wheat protein. In a detailed study of a 13½ year old girl with severe growth failure and the typical metabolic lesion of celiac disease, he was able to demonstrate only a moderate defect in fat absorption and no interference with absorption of protein or carbohydrate. When a gluten-free diet was administered, rapid growth resumed before the enteropathy or anemia was significantly changed.

Other disorders of the gastrointestinal tract, such as regional enteritis, ulcerative colitis, jejunocolic fistula, and other shunts have all resulted in growth failure. These disorders may escape detection for many years, and the patients are often erroneously diagnosed as pituitary dwarfs. The possible role of the pituitary in mediating the effects of malnutrition upon growth and development was discussed on page 926.

Before the advent of slow-acting protamine zinc insulin, *diabetic* children were frequently dwarfed and showed hepatomegaly. This is now unusual except for a peculiar syndrome of dwarfism, hepatomegaly and obesity associated with diabetes mellitus which is referred to as the Mauriac syndrome.[19] These patients are labile diabetics with a history of poor control. The dwarfism is thought to be related primarily to nutritional factors, although pituitary factors have been incriminated. The physiopathology of this syndrome still remains largely obscure.

INBORN ERRORS OF METABOLISM

Many of the inborn errors of metabolism such as galactosemia, hepatic glycogen storage disease, cystinosis, vitamin-D-refractory rickets,

oxalosis and the De Toni-Fanconi syndrome result in retarded growth. Although these conditions are rare, two of the more common are elaborated upon below.

GLYCOGEN STORAGE DISEASE

The clinical features of glycogen storage disease consist in hepatomegaly, hypoglycemia, acidosis, hyperlipemia, and a diabetic type of glucose tolerance curve. Some of these patients are able to sustain prolonged hypoglycemia without clinical symptoms. Growth failure commonly is an associated abnormality. Cori and Cori[7, 8] have demonstrated that the main defect is a diminished or absent glucose 6-phosphatase activity in liver and kidney.

The cause of the growth failure in this disorder is not clear. Recent findings of Schwartz, Ashmore and Renold[32] indicate that there may be delayed utilization of glucose due to peripheral starvation which results from inability of the liver to produce glucose. This hypothesis would explain not only the diabetic glucose tolerance curve and the mobilization of fat resulting in lipemia, but also the failure of growth. The effects of chronic acidosis per se on growth are not known.

GALACTOSEMIA

Galactosemia, an inborn error of metabolism, is a well known cause of growth failure in infancy. In addition to physical and mental retardation, other characteristic clinical features consist in hepatomegaly, mental retardation, prolongation of physiologic jaundice, and cataracts.

Examination of the urine shows a reducing substance which can be identified as galactose. Albuminuria and aminoaciduria are constant findings. In severe cases the course may be fulminating, with death in the newborn period; mild cases may not come to the attention of the physician until cataracts develop or a reducing substance is detected in the urine. Ritter and Cannon[31] have reported a child in whom galactosemia was first diagnosed at the age of $4\frac{9}{12}$ years who, in addition to cataracts and melituria, was undernourished and in the third percentile for height.

This disorder has now been shown to be due to deficiency of a specific enzyme. Removal of milk and milk products from the diet at an early age will result in resumption of normal growth.

MISCELLANEOUS CONDITIONS

Some recently described conditions in which growth failure is a prominent feature are described below.

IDIOPATHIC HYPERCALCEMIA OF INFANCY

Idiopathic hypercalcemia of infancy is a new clinical entity which has received considerable attention in the European literature. Although only one case has been reported in the United States thus far,[11] the authors have heard of as yet unreported cases in various American pediatric centers. These infants characteristically exhibit hypercalcemia and its associated symptoms, such as anorexia, vomiting, constipation, irritability, hypotonia and weight loss. The more common physical findings are malnutrition, mental-motor retardation, a peculiar facies, heart murmur, muscular hypotonia, apathy and irritability, hypertension and hyperreflexia. Growth failure has been a constant finding in all instances of the severe form of the disease.

In addition to hypercalcemia, laboratory findings include azotemia and other evidence of impaired renal function. The serum phosphorus level is normal, and this is an important feature distinguishing this condition from primary hyperparathyroidism that may occur in rare instances in this age group. There appears to be a mild and a severe form of the disease. The etiology of the disorder is unknown. Hypersensitivity to vitamin D with excessive calcium absorption has been suggested as the basic abnormality for this disease, but this has not been proved.[11]

LEPRECHAUNISM

In 1954 Donohue and Uchida[12, 13] described two sisters with a peculiar external appearance and growth failure. Because of the elfin-like facies in their patients, these authors proposed the colorful term "leprechaunism" for this disorder. Evans[15] has described two children thought to be instances of this disease complex. In addition to growth failure and delay of epiphysial maturation, these children show a characteristic facies in infancy, with large, low-set ears, big, wide-set eyes, and hollow cheeks, negroid features and hirsutism. Other abnormalities include enlargement of the breasts, clitoris, liver and ovaries. The ovaries show many large follicular cysts; the kidney tubules are dilated and plugged with granular masses containing calcium. A sixfold increase of insulin content of the pancreas was found in one instance, and an abnormally prolonged fall in blood sugar after administration of insulin has been reported in two other instances. The four cases were females. The pathogenesis is unknown; it has been suggested that these children may combine anomalies of anatomical development with abnormalities caused by ovarian hypersecretion starting in fetal life.

CONGENITAL HEART DISEASE

Growth deficiency, and even notable dwarfing, have long been known to occur in conjunction with heart disease. The nature of this relationship is not clear; many authors have suggested that the hypoxia of critical tissues leads to diminished growth.

Campbell and Reynolds[5] studied the physical development of 400 children with congenital heart disease. They found that the children were slightly below the expected height. Children of one year of age were more than 1 inch below the average.

The degree of cyanosis could be roughly correlated with the degree of stunting, the latter being greatest in severely cyanotic children, intermediate in those with mild cyanosis, and slightest in acyanotic patients.

In an individual case the situation may be more complicated. Children with congenital heart disease frequently also have other congenital anomalies which have to be evaluated with regard to stunting of growth. As an example, we refer to the situation in gonadal dysgenesis, discussed on page 936. This disorder is almost always associated with stunting of growth, and frequently with congenital heart disease. Since deficiency of growth is present in these cases, regardless of the presence of congenital heart disease, it is clear that in this instance the heart disease, with or without cyanosis, may not be the cause of dwarfing. As is pointed out on page 936, the gonadal dysgenesis, stunting of growth and malformation of the heart must be regarded as coordinated, independent, congenital anomalies.

DELAYED ADOLESCENCE

Practically every disorder described above has been, in many instances, misdiagnosed as pituitary dwarfism. Likewise, many children with growth failure in whom study fails to reveal the cause of the dwarfism are indiscriminately labeled pituitary dwarfs. It is important to keep in mind the great variation in growth patterns of perfectly normal children. Most of the disorders reviewed in this paper can be diagnosed at a glance or by the use of carefully selected diagnostic studies. There still remains a relatively large group of children with retarded growth in whom the diagnosis is not clear. Most of these patients represent expressions of normal variability of growth.

These children are frequently below the third percentile for height throughout childhood, but appear perfectly normal in all other respects. The bone age is frequently retarded and corresponds to the height age rather than to the chronologic age. Studies of endocrine function usually yield completely normal results. This group of patients fails to show the usual puberal growth spurt, or fails to mature sexually at the same

time as their contemporaries. However, at 16 or 17 years of age or later, puberty finally begins and maturation is eventually complete. Once begun, growth and maturation may be rapid. On the other hand, growth and sexual development may take place slowly over a period of years, owing to the fact that the bone age is retarded and epiphysial fusion occurs late. The height eventually attained by the majority of these children is within the normal adult range. There appears to be a delay in the activation of the hypothalamo-pituitary-gonadal system, and not a specific defect of a gland. It is apparent that it may be difficult, if not impossible, to distinguish some of these patients with slow growth and maturation from those with true pituitary dwarfism until well past the teen-age years. Since the children with delayed adolescence will eventually mature into normal adults, it is best to defer therapy as long as possible. Serious emotional disturbances often develop during the years when their contemporaries are undergoing normal adolescent changes, and the physician may justifiably attempt a course of therapy to stimulate maturation. A detailed discussion of the use of gonadotropins or androgens, for this purpose, as well as of possible untoward effects from such medications, is beyond the scope of this review.

EDITOR'S NOTE. Practically all chronic diseases or developmental defects of any system or organ which are severe enough and permit life to go on for a sufficient time will be attended by dwarfism or at least retarded statural growth. W.A.R.

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OBESITY IN CHILDHOOD

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Fifteen to 25 per cent of patients referred to a pediatric endocrine clinic are obese. Though this figure suggests that obesity in childhood is common,[8] it indicates even more clearly how widespread is the belief among referring pediatricians, school physicians and hospital residents that obesity is caused by dysfunction of the endocrine glands and should be treated by an endocrinologist. Thus the obese girl is thought to be hypothyroid, and the prepuberal boy whose genitals are obscured by large perineal and suprapubic fat pads is given a presumptive diagnosis of "Froehlich's syndrome." The endocrinologist to whom these children are referred is usually convinced that "the only glands concerned with the development of obesity are the salivary glands." Hence obesity is due to "overeating," which is something out of the province of endocrinology and for which there is no effective treatment. Unfortunately, by oversimplifying this problem and adopting a pessimistic attitude toward its treatment, the endocrinologist himself is frequently responsible, in part, for the poor results of therapy.

It is true that the obese child as well as the obese adult rarely shows any evidence of endocrine disease, and it is undeniable that the fat child has consumed in the past or still consumes more calories than are

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needed for energy expenditure, even though the parents may not be impressed by this fact. But it remains to be explained why the obese child, unlike the nonobese, fails to adjust his caloric intake to his energy expenditure. This problem of appetite adjustment has only recently been examined experimentally. The results of these studies lead to the inescapable conclusion that there may be multiple causes of obesity which, strictly speaking, should no longer be considered "exogenous" or "endogenous," but rather a combination of the two.[11, 15]

THE REGULATION OF FOOD INTAKE AND CALORIC EXPENDITURE

Appetite or caloric intake is influenced by many voluntary and involuntary processes in the body, not all of which are completely understood. We do know, however, that there are two paired centers in the ventromedial nuclei of the hypothalamus intimately concerned with the unconscious (i.e., subcortical) regulation of appetite.[1, 3] Destruction of the more medial portion of this area in experimental animals leads to hyperphagia and obesity; damage to the more lateral nuclei on both sides results in profound anorexia. Accordingly, there are paired lateral "appetite centers" and medial "satiety centers." These centers receive afferent impulses via the autonomic nervous system from various organs in the body. Hunger contractions of the empty stomach, for example, signal the need for food, whereas gastric distention reflexly leads to loss of appetite.

A large number of systemic diseases depress appetite—febrile illnesses, liver disease, certain vitamin deficiency states, to mention only a few. Striking changes of appetite are seen in various endocrinopathies, for anorexia is common in hypothyroidism and is often marked in Addison's disease, whereas hyperphagia is characteristic of hyperthyroidism and diabetes mellitus, and often follows the administration of steroid hormones, such as cortisone, the androgens and estrogens. In these latter instances the hypothalamus would appear to be affected by generalized metabolic alterations rather than by reflex nervous stimulation. Mayer[11, 12] has attempted to explain this by means of the "glucostatic theory" of appetite regulation. According to this theory, the appetite center is stimulated, or the satiety center is inhibited, by a fall in the amount of utilizable glucose circulating in the blood to the brain. A decreased supply of glucose to the hypothalamus may result from systemic hypoglycemia, as in postprandial or reactive hypoglycemia, often found in hyperthyroidism, or following the administration of insulin, but it can also occur even when the blood sugar level is elevated, as the result of disturbed glucose utilization, due to insulin lack (diabetes mellitus), interference with insulin action (by means of corticosteroids) or other disturbances of carbohydrate metabolism. According to the

glucostatic theory, almost any generalized metabolic derangement might be expected to affect appetite and, accordingly, food intake, by altering the supply of glucose to the ventromedial hypothalamus or the ability of the hypothalamus to metabolize carbohydrate.

In addition to stimuli received from lower neural centers and via the blood stream, the hypothalamic appetite centers are affected by other stimuli arising from the cerebral cortex. Thus psychological or voluntary cortical factors are integrated with involuntary, physiological factors at the level of the hypothalamus, where the stimulus of the former may override that of the latter. Take as an example the common observation that arguments at the dinner table may lead to loss of appetite even though the person is hungry, or the fact that for a time at least, both children and adults will prefer to go hungry rather than eat food which is displeasing to them in appearance, consistency or taste. The importance of visual and oropharyngeal stimulation in the production of satiety has been well documented in experimental animals. Under standard conditions an animal will ingest a certain amount of food and no more. If the animal is offered half this amount before the usual mealtime, he will eat only the remaining half a little later, at the usual time. If, however, he is given half the usual feeding by stomach tube, he is less satisfied and will eat more than the remaining half when it is placed before him subsequently.[7] At this point, obviously, habit and custom also enter to play an important role in determining not only the type, but also the quantity of food ingested.

With all these factors operative, the healthy child normally so adjusts his food intake to energy expenditure that graphs can be drawn and tables compiled of average weight for age or ideal weights for height. In dealing with this balanced equation of intake and output undoubtedly less attention has been paid to energy expenditure than to caloric intake,[2, 9, 14] perhaps because it is more difficult to measure the former than the latter in the growing child. Perhaps the even greater difficulty of measuring the energy expenditure of exercise explains why so much emphasis is usually placed on the energy consumed to maintain basal metabolism, which, theoretically at least, is far easier to calculate. The following figures, applicable to boys and girls between the ages of one and 15 years, illustrate the true state of affairs:

RELATIVE CALORIC EXPENDITURE

Basal metabolism	40%
Growth, specific dynamic action of food, etc.	30%
Exercise	30%

Accordingly, the basal metabolism accounts for only 40 per cent of the total energy expenditure of the child. Even this figure needs scrutiny. Since basal metabolic expenditure is arbitrarily defined as the consumption of energy at rest, not during sleep, it is influenced by the degree of

muscle relaxation and thus by relative muscle mass. In the adult 10 per cent less energy is spent in the sleeping state than at rest, in the child 15 to 16 per cent.[13] It has been shown experimentally that the change from sedentary existence to a program of systematic exercise, which increases muscle tone and mass, can raise the basal metabolism of an adult 20 to 40 per cent.[13]

At the same time the amount of calories expended as the result of muscle activity is usually greatly underestimated. The infant may increase his energy output 200 per cent above basal expenditure merely by vigorous crying; crying and kicking may raise the total daily energy expenditure by 25 to 50 per cent. Since muscle training decreases caloric expenditure by increasing efficiency, it follows that the child usually expends more energy than the adult in performing the same amount of work (walking, running, climbing stairs, and so on). It is rarely appreciated that children and adults spend most of their time lying, sitting and standing, and that energy expenditure for this usually ignored "exercise" varies greatly from person to person.[2]

Several investigations of the hyperglycemic-obese syndrome in mice emphasize the fundamental importance of actually measuring activity to define its contribution to weight control and the development of obesity.[11, 12] The hyperglycemic-obese syndrome is transmitted as a recessive gene. The affected mice become markedly obese, ultimately weighing two or three times as much as their litter mates. Balance studies demonstrate that normal adult mice maintain body weight by consuming an average of 20 calories daily, of which 10 are spent on basal metabolism, 2 on the specific dynamic action of food, and 8 (40 per cent) on activity. The obese mice with this syndrome ingest only 20 per cent more calories than their litter mates, which is an amount insufficient to cause such a tremendous, rapid weight gain. The inactivity of these mice is really more striking than their excess appetite and is evident even before the obesity becomes notable. Because the obese mice are only 1/50 or 1/100 as active as their litter mates and do not adjust their appetite correspondingly, they have available for fat storage an excess of 12 calories daily, only 4 of which are attributable to extra food consumption, while 8, or twice as many, are due to inactivity. By selective breeding it has been possible to produce mice which carry both the "obesity gene" and the "waltzing gene." These animals, constantly exercising, do not become obese!

Obesity cannot be produced in experimental animals by forced feeding alone.[11] There must be a genetic predisposition, as in the inactive, obese-hyperglycemic mice, or a variety of traumatic agents must be used along with forced feeding, such as surgical damage to the hypothalamus, injections of gold-thioglucose, thyroidectomy or prolonged administration of protamine zinc insulin. In all these instances, even

though abnormalities of fat synthesis and mobilization can be demonstrated, storage fat is nevertheless consumed when the animal's caloric intake is restricted below the calculated energy requirements. Weight loss occurs in direct proportion to the degree of caloric deficit. Not only decreased intake, but also increased energy expenditure, leads to a loss.

CLINICAL EXPERIENCE VIEWED IN THE LIGHT OF LABORATORY INVESTIGATION OF OBESITY

There is much evidence to indicate that genetic factors play a role in the development of obesity in man as well as in experimental animals. Just as certain strains of domestic animals put on more fat than others by eating more when offered a free choice of diet, are selectively bred for this purpose, and penned up to prevent them from "running off fat," so certain persons and even whole families seem prone to ingest more calories than they expend, and as a result become obese. In human beings this is due in part to the establishment of undesirable food habits at an early age; hence it is not surprising to find that the parents of obese children are often obese themselves.[11] This does not explain, however, why identical twins, raised under different environmental circumstances, have almost identical weights. Older clinicians emphasized the broad, stocky skeletal build of children who subsequently became obese and felt that there was a constitutional element in this disease.

The significance of endocrine function in the regulation of appetite and the production of obesity is well known from animal experimentation, especially from the studies of the obese-hyperglycemic syndrome in mice. In obese human subjects, in contrast, there is rarely any obvious evidence of endocrine disease, but in our present state of knowledge the word "obvious" should perhaps be underlined. Only three distinct endocrinopathies are known to be associated with the development of obesity, namely, hypothyroidism, Cushing's syndrome and insulin-producing tumors of the pancreas. Such tumors are extremely rare in childhood and do not merit further discussion. Cushing's syndrome is also rare in the pediatric age range. Hypothyroidism, though relatively common in childhood, usually leads to diminution in appetite rather than hyperphagia.[16] *It is almost never associated with a significant degree of obesity.* Usually simple clinical inspection is adequate to rule out either Cushing's syndrome or hypothyroidism. Both diagnoses should be promptly discarded when the examiner learns from the history that the child has continued to grow in height as well as girth and when measurement discloses that the patient's height is above the fiftieth percentile for age. Cushing's syndrome and hypothyroidism in childhood of sufficient severity to "cause" obesity both lead to an arrest of linear growth. The obese child, in contrast, is almost always

taller than average for age, and his bone age is frequently advanced one to two years.[4] The diagnostic term "Froehlich's syndrome" should be abandoned. In all probability the patient described by Froehlich was neither obese nor hypogonadal due to pituitary disease, but was rather a preadolescent obese boy with a pituitary tumor.

Laboratory studies have clearly related the development of obesity in experimental animals to muscular inactivity unaccompanied by a proportionate reduction in caloric intake. Most obese children are almost as inactive as the experimental animals, avoiding sports and preferring sedentary recreations such as reading, watching television, building model airplanes or drawing. Usually they eat as they sit, and it is unfortunate nowadays that they do not even have to walk to the local theatre to see the movies, but can see them in their own living room.

Various factors seem to be at work to produce this inactivity. Wilkins[16] believes that many of these children are awkward from the start, owing to poor muscle coordination, and, because of their inability to compete in sports, avoid exercise. Family attitudes towards sport undoubtedly influence the child as well. Many obese children are depressed about their appearance and go to almost any length, short of real exercise, to avoid criticism by their classmates. For example, they will refuse to go swimming because of the need to wear a bathing suit. As their obesity increases, their activity frequently decreases even more, but not so the appetite for food. The decreased opportunity for outdoor play, coupled with compulsory attendance in school, largely accounts for the fact that the obese child puts on most of his excess weight during the winter months.[9]

Laboratory studies have shed little light on the psychologic factors stimulating or permitting caloric intake in excess of expenditure, which is unfortunate, for these poorly defined factors seem to play an important role in the development of obesity in most children and are clearly involved in the obese child who is taken to the physician primarily because of an emotional disturbance. Hilde Bruch[5] was among the first to emphasize the importance of emotional immaturity and maternal overprotection in the development of childhood obesity. Seventy per cent of her patients were only children or the youngest child; in many instances the obese child was born after the death of a sibling and was thus given extra mothering, which included extra food. The parents she interviewed not only greatly overestimated the amount of food their children needed and encouraged overeating early in life, thus setting up a habit pattern, but also in many instances seemed unable to express love and affection for the child except through the offering of food. To these parents overeating was a safeguard against disease, a form of security. The obese child was conditioned by such parental attitudes to remain obese.

THE TREATMENT OF CHILDHOOD OBESITY

Theoretically, it would seem important to recognize and treat obesity at as early an age as possible before the "tendency to obesity"[10] becomes firmly ingrained as a way of life. In actual practice, treatment is rarely effective until the child is sufficiently mature to adhere to a starvation diet, or, in other words, is willing to undergo nutritional privation in order to achieve an important social goal. For this reason, unless the child is at least 11 or 12 years old, the most that can be hoped for from treatment is the prevention of continued, rapid weight gain. In the growing child this actually represents weight reduction. The parents of the young obese child should be given dietary advice, but often do not heed it; or if they do, the child is unable or unwilling to cooperate with the parents in adhering to a diet. It is usually futile to focus attention upon obesity if neither the parent nor the child is concerned about it, or if it is obvious that the more serious problem requiring attention is a behavior disturbance.[6] Occasionally even such children will lose weight if the whole family goes on a diet.

The emotional disturbances involved in the development of obesity during childhood seem to be more amenable to casual psychotherapy by the general practitioner than they are in the obesity of adult life. Occasionally one can date the onset of obesity from a single emotional disturbance in a child's life, although in most instances these conflicts have developed early in childhood, and have become obscured by the passage of time.

Eric B. was referred to the Endocrine Clinic at age 13½ in November, 1956, because of suspected delay in sexual development and obesity. Neither parent was obese, nor was there a family history of obesity. Eric was of average height and weight at age 11 years when the family moved from central Philadelphia to a suburb. At this point the boy lost all contact with his former classmates and for this reason disliked the new school he was forced to attend. He gave up most of his usual outdoor activities, became moody and developed a gradually increasing appetite. His diet was estimated to contain 3000 to 3500 calories a day. Recently the parents also became concerned about his small genitals, and he himself grew extremely self-conscious about his appearance. Physical examination revealed a boy of average height for his age, weighing 120 pounds, 30 pounds in excess of the average for his height. The obesity was generalized. The penis and testes were normal for an early stage of adolescence. It was explained to Eric that he was developing normally, but that his obesity caused his genitals to appear smaller than they actually were. He accepted the explanation that his obesity resulted from a combination of inactivity and overeating, and he seemed interested in trying a 1500-calorie diet which was outlined in detail. No drugs were prescribed. At a return visit one month later Eric weighed 107 pounds, at the end of 2 months 99 pounds, after 3 months 97 pounds, and finally after 4 months of diet, 92 pounds, during which interval he had grown an inch in height. Not only had he eaten less, but also he had increased his activities and become more interested in sports. Both the parents and Eric were proud of this achievement, and, responding to parental encouragement, Eric wished to lose even more weight if we thought it desirable.

It is frequently stated that since a child will not adhere to a starvation diet, it is best to restrict the caloric intake only about 20 per cent.

This will undoubtedly prove effective if the child is given a definite, prescribed diet and detailed advice, but vague dietary instructions, such as the need to eliminate second helpings and to avoid fatty or starchy foods, are of little value. The parents and the child frequently interpret generalities much too liberally, and they even seem to feel that the physician who is content to give so little instruction is insufficiently interested in their problem. It is wise to have the patient record at home the type and amount of food eaten on three consecutive days before prescribing a diet. From such data only a general idea of total caloric intake is obtained, but the effort involved is nonetheless worth while, for the parents of the child acquire some idea of how much he actually eats, and they grow to feel that the physician is really interested in helping them.

The reduction diet prescribed should provide adequate (15 to 20 per cent) protein, sufficient bulk, and at least 500 calories fewer than one estimates are necessary to maintain weight, but should otherwise be adjusted to the patient's likes and dislikes. The number of calories required may be estimated from the following round figures for normally active boys and girls:

Age	Caloric Intake	CALORIC EXPENDITURE		
		Basal (40%)	Growth, etc. (30%)	Activity (30%)
5 years	1500 cal.	600	450	450
10 years	2500 cal.	1000	750	750
15 years	3000 cal.	1200	900	900

The obese 10 year old boy, for instance, because he is inactive expends only 10 per cent of the appropriate (2500) caloric intake for exercise. Accordingly, he can maintain weight on a 2000-calorie diet per day. For him a 1500-calorie reducing diet should be prescribed. This daily deficit of 500 calories will result in the loss of about 1 pound of body weight each week, a rate of loss which should be explained to both the child and the parent, who may otherwise expect much more.

Some attempt should be made to direct the child into social activities demanding a greater expenditure of energy—dancing rather than piano lessons, for example. A worth-while and tangible reward for losing weight should be offered every obese child, preferably one which encourages outdoor activity or social adjustment, such as a bicycle or a week at summer camp.

Some children are helped by the judicious prescription of anorexigenic drugs along with a reduction diet. We feel it important, however, that the child first learn what he or she can accomplish by diet alone, for this is an invaluable educational experience. It should also be clearly

explained when drugs are used that they only help strengthen the will power necessary to adhere to a weight reduction diet and do not themselves miraculously cure obesity. Amphetamine has been widely used in the past, with variable success. Some patients develop tolerance to the drug, others complain of insomnia from it. A new preparation, Phenmetrazine hydrochloride,* may be worth a trial because of its reputed lesser tendency to cause side effects. In our experience it has proved valuable only when the patient has already demonstrated that he has sufficient motivation to lose some weight by diet alone and then later becomes discouraged or depressed.

No therapy, be it dietary advice or the prescription of drugs, is as effective in helping the obese child lose weight as the physician's genuine interest in the general problem of obesity and the specific problem which the individual child presents. The physician who wishes to help these obese children should deliberately cultivate an interest in both. He should be willing to see the child and the parents at frequent intervals and to discuss the many small problems which arise. If the child is old enough to come in unaccompanied by the parents, as he should be encouraged to do, the physician can establish a friendly relationship with the child more easily, perhaps. But contact with the parents is equally important, since many of them also are overweight and need dietary advice as much as their children. Obesity is a family problem. When the parents grow to realize this fact and the importance of setting an example, they frequently do more than the physician can to help the obese child lose weight.

EDITOR'S NOTE. The writers stress newer knowledge of genetic factors—obesity and "waltzing" genes in rats—which is an interesting development.

The necessary interest by the physician is a "sine qua non." Primarily the patient must be interested in losing weight; otherwise he is wasting his time. When the physician points out to him the desirability of at least not gaining more or losing and the patient realizes this, the "battle" is joined. It begins only when the patient decides and lends himself to weight control. When the physician shows interest and sympathetic understanding, establishing a healthy liaison for therapy, the patient knows he has someone to share the burden, and the "battle" is being won. Only the patient can win it. The physician gives experienced advice. He must police the patient by seeing him frequently in the early months of therapy, to help and encourage him.

Some other helpful comments: As the authors state, do not start with a starvation diet; this sudden, radical reduction of calories is discouraging, especially to a child. If the child has been taking 3500 calories and requires only 2250, condition him with 3250 for two weeks and reduce this by 250 or 500 calories every two weeks until desired weight loss occurs. Give portions after school and before retiring. A basal caloric intake may be necessary eventually. Sometimes it is helpful to start with a qualitative reduction diet for a few weeks before starting a quantitative diet. Suggested diets are given by Matthew M. Steiner (PEDIATRIC CLINICS OF NORTH AMERICA, May, 1955, pp. 553–65). Dr. Eberlein also uses individualized diets prescribed by local dietitians. Keep up exercise. Success can be had in possibly two thirds of patients by the combination of such psychotherapy, diet, exercise and drugs.—W.A.R.

* Preludin, Geigy Chemical Co.

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LABORATORY DIAGNOSIS IN PEDIATRIC ENDOCRINOLOGY

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The purpose of this article is to indicate the principles of certain laboratory diagnostic methods presently available and to discuss their value and reliability in pediatric endocrinology. Recently, Wilkins[75] has reviewed this subject in detail, and the present evaluation of techniques will be based on the experience obtained by his group at the Endocrine Clinic of The Harriet Lane Home.

The most direct measurement of the functional status of an endocrine gland is the determination of its rate of hormone production. Since it is usually impossible to estimate the hormonal content of the efferent vein blood of the gland in question, the next best approach is the study of its excretion rate in urine and/or feces. Before elimination, however, the compound is often metabolized, so that it is necessary first to determine the nature of its catabolites if excretion is to be related to production. Means of separating these catabolites from nonspecific material must then be found and methods devised for their quantitative measurement. Some techniques take advantage of a specific physical or chemical property of the hormone, while with others one is obliged to study some of the known biological effects of the hormone on test animals.

Hormones have definite physiologic properties; pathologic variations in their production will produce alterations in the concentration of certain constituents of the body fluids. For example, the determination of blood glucose provides valuable information about the over-all status of the hormones and factors which control glucose metabolism.

ANTERIOR PITUITARY HORMONES

The pituitary hormones are proteins or polypeptides, the structures of most of which have not yet been determined. Therefore estimation of the concentration of these compounds in body fluids cannot be accomplished by chemical techniques, and bioassays are made.

The Gonadotropins

This is probably not a single factor, but a mixture of several components: the follicle-stimulating hormone (FSH), which activates the growth of ovarian follicles and the germinal epithelium of the testis; the luteinizing hormone (LH), which stimulates the development of the corpus luteum in the female and the Leydig cells in the male; and the luteotropic hormone (LTH), which maintains the function of the corpus luteum and is probably identical with prolactin.

Method of Assay of Human Urinary Gonadotropins. This question has been reviewed by Hamburger[31] and more recently by Albert.[2] First, the hormone must be concentrated, and kaolin adsorption appears to be the method of choice.[8] This is followed by an elution of the protein from kaolin, using 1N ammonium hydroxide. The eluate is brought to pH 5.5 with glacial acetic acid, and the protein is then precipitated by the addition of 95 per cent ethanol. The test animals may be immature rats or mice.[34] The extract is injected over a period of three or four days, and 24 hours later the animals are sacrificed. The weight of the ovaries or uterus is then determined.

Normal and Physiological Variations. Normal males and females between 20 and 45 years of age excrete 6 to 52 mouse units (5 to 15 rat units) daily. Urinary gonadotropins are not detected in the urine of children before the age of puberty,[2] but may often be detected in girls six months to one year before the first menses. Physiologically, negative results are often found at the beginning and end of the cycle, and positive values are usually obtained at midcycle;[16] however, Albert[2] could not demonstrate a definite pattern from cycle to cycle or from subject to subject. When using a test thought to be specific for LH,[40] McArthur was able to detect a peak at mid-cycle.[41]

Abnormal Values. There is characteristically a complete absence of urinary gonadotropins in cases of hypopituitarism. This may be a specific gonadotropin deficiency, which is rare, or it may be seen in association with other pituitary tropic hormone deficiencies. The latter group includes hypopituitary dwarfism, Sheehan's syndrome caused by postpartum infarction and necrosis of the hypophysis, and Simmonds' disease. These levels may be low or absent in cases of malnutrition as

well as in some cases of severe emotional disturbance (e.g., anorexia nervosa).

Urinary gonadotropins are elevated in cases of gonadal insufficiency in which pituitary function is adequate. This is seen after surgical castration or in eunuchoidism due to infectious disease, as well as in cases of gonadal dysgenesis. The so-called Turner's syndrome and Klinefelter's syndrome fall into the latter group. In "constitutional" sexual precocity, urinary gonadotropins are theoretically positive before the physiologic age of puberty; however, they are often negative until the age of 10 or 12 years. In sexual precocity of neurogenic origin the levels are thought to reach normal adult levels. In cases associated with the adrenogenital syndrome they are negative, although they become positive under cortisone therapy when the general level of maturity, as measured by the bone age, is about 11 to 13 years.

REMARKS. Gonadotropins should not be expected to be detected before puberty. As in most bioassays, the actual figures given for gonadotropin levels are rather inaccurate, and one must be prudent in the interpretation of such values, especially when one studies the fluctuations in concentration in an individual case under various conditions. Very high levels are of great diagnostic importance, while low or negative values have little significance, since the assay is not sensitive enough to distinguish between low-normal and pathologically low levels.

Thyrotropic Hormones

The bioassay of thyrotropic hormone has been reviewed by Albert[1] and Turner.[74] Various test animals have been used, such as the guinea pig, chick, hypophysectomized rat and tadpole, but none of these assays are very satisfactory. The tadpole technique developed by D'Angelo and Gordon[17] can apparently detect the minute amounts of TSH present in the blood of man. In recent years efforts have been made to develop methods using the effect of TSH on I^{131} thyroid uptake in the hypophysectomized chick.

Adrenocorticotropic Hormones

In discussing the various methods proposed for the bioassay of ACTH, Greenspan et al.[29] concluded that the adrenal-ascorbic acid depletion test, as standardized by Sayers et al.,[63] is the most sensitive and accurate technique. More recently Nelson and Hume[50] devised an interesting method based on the determination of the effect of ACTH administration on 17-hydroxycorticosteroid concentration in adrenal vein blood of hypophysectomized dogs. High levels of ACTH have been detected in the plasma of addisonian patients, but no activity could be demon-

strated in the blood of normal subjects by any of the techniques mentioned above.

Melanocyte-Stimulating Hormone (MSH) and Growth Hormone

An assay using isolated frog skin has been described,[65] and the 24-hour urinary excretion in normal adult males and females ranges from 7.5 to 47.5 units.

Among the various techniques proposed for the measurement of growth hormone, the response of the proximal tibial epiphysis in the hypophysectomized rat seems to be satisfactory.[28] Neither of these hormones is determined routinely.

POSTERIOR PITUITARY LOBE HORMONES

The two hormones isolated from the posterior lobe of the hypophysis, oxytocin and vasopressin, have recently been synthesized by du Vigneaud and collaborators.[20] Only the latter one will be discussed here.

Stein et al.[72] reviewed the various methods of antidiuretic hormone assay and summarized the results obtained. These bioassays are rather complicated techniques, and their diagnostic value is open to question.

The diagnosis of diabetes insipidus may be suspected in patients with definite polydipsia, polyuria and low urinary specific gravity. Several tests have been devised to differentiate this condition from psychogenic polydipsia, such as the effect of fluid restriction on urinary specific gravity, the hypertonic saline test of Carter and Robins,[11] and the nicotine test. A therapeutic test with a posterior pituitary preparation controlled by a placebo test may also be useful.

HORMONES OF THE ADRENAL CORTEX

Cortisol is the main corticosteroid secreted in man, but small amounts of corticosterone are also produced.[60] In some abnormal conditions significant quantities of other corticosteroids may be secreted, such as Reichstein's substance S. The electrolyte-regulating factor of the adrenal has been shown to be aldosterone.

Adrenal androgens may be divided into 3β- and 3α-hydroxyl compounds. The latter group may be further subdivided into compounds with and without an oxygen at carbon-11. The 3β-hydroxyl steroids and 3α-hydroxyl-11-oxygenated steroids are thought to originate only in the adrenal cortex.

Estrogens and progestins are also secreted by the human adrenal.

Clinical tests, bioassays and chemical determinations of the various adrenal steroids are summarized in Table 10. Only the most significant of these tests will be discussed.

TABLE 10. *Diagnostic Methods for Steroid Measurement*

STEROIDS	CLINICAL TESTS	URINE		BLOOD
		Bio-assay	Chemical	
Corticosteroids	Fasting blood sugar Tolerance tests	Liver glycogen in fasting adrenX rat Work test	17-OH-CS 17-ketogenic steroids (response to ACTH)	17-OH-CS (response to ACTH)
Androgens	Size of prostate, phallus Signs of hirsutism	Capon comb test Prostate, sem. ves. of castrated rat	17-KS (column chromatography) DHA (Allen Test)	17-KS
Electrolyte regulating hormone (aldosterone)	Serum Na, K, CO_2, Cl Sweat, saliva Na/K ratios Diuresis test	Na or Na/K in urine of adrenX rats	Chromatographic separation Fluorescence or BTZ	
Estrogens	Vaginal smear Endometrial biopsy	Vaginal smear of castrated mice Uterine weight of immature mice or rats	Fractionation Fluorescence or Kober reaction	
Progestins	Basal temperature Endometrial biopsy Vaginal smear	Hooker-Forbes test	Pregnanediol Pregnanetriol	Hooker-Forbes test

Plasma 17-Hydroxycorticosteroids (17-OH-CS)

METHODS OF ASSAY. The technique of Nelson and Samuels[51] is widely used: the steroids are extracted from the plasma by chloroform or methylene chloride, chromatographed on florisil columns and measured by the reaction of Porter and Silber.[55] In the method of Silber and Porter[67] and its modification by Peterson[54] the column chromatography is not carried out. In order to obtain purer extracts, a benzene:water:-chloroform partition may be of value.[21]

SIGNIFICANCE. These tests measure only the steroids with a 17,21-dihydroxy-20-ketone, and, therefore, corticosterone is not measured by this assay. Furthermore, only the free 17-OH-CS are determined, but a β-glucuronidase hydrolysis of the plasma residue permits the measurement of some of the conjugated steroids.[7]

NORMAL VALUES. The 8 to 9 a.m. average is 15 micrograms per 100 ml. of plasma (range: 8 to 20 micrograms). Because of marked diurnal variation of the levels,[48] it is most important to collect the control blood specimens at 8 to 9 a.m.

It has been suggested that the fetus produces little corticosteroid and that the concentration of these hormones in the cord blood is merely the reflection of maternal levels.[47] During the first few days of life the plasma levels in the newborn are low,[33] but normal adult levels are attained within the first few weeks. After the neonatal period the total production of hormone seems to be related to body surface.

ABNORMAL VALUES. The 17-OH-CS are decreased in Addison's disease, pituitary deficiency involving adrenocorticotropic hormone, administration of potent corticosteroids (e.g., 9-fluoro-cortisone), and frequently in congenital adrenal hyperplasia.

The concentrations are increased in Cushing's syndrome (see Table 11), ACTH administration, medical and surgical stress and, to a less degree, severe emotional stress.

ACTH TEST. In certain cases it is of value to test the response of the adrenals to ACTH. Twenty-five milligrams of ACTH diluted in 300 to 500 ml. of normal saline or glucose solution are given intravenously over a period of six hours. Blood samples are collected just before the infusion, and at two, four and six hours. Normally, the average values are, at two hours, 26 $\pm$ 6 micrograms; at four hours, 36 $\pm$ 10 micrograms; and at six hours, 41 $\pm$ 12 micrograms.

In Addison's disease the control value might be subnormal, but no response to ACTH is obtained.[61] In hypopituitarism with hypoadrenocorticism a slight response is often observed; in such cases the administration of 25 mg. of long-acting ACTH every 12 hours for a period of four or five days will usually cause a normal rise of plasma and urinary 17-OH-CS levels. In Cushing's syndrome due to adrenocortical carci-

TABLE 11. *Classification of Cases of Hyperadrenocorticism*

ETIOLOGY				HORMONAL DYSFUNCTION			
				Androgens	Corticosteroids	Electrolyte-Regulating Factor	Estrogens
Cushing's Syndrome	1. Bilateral adrenal hyperplasia (related or not to hypothalamic lesion or basophilic adenoma of pituitary)			+ or N	+++	+ (?)	N or +
	2. Unilateral adrenal adenoma			− or N	+++		
	3. Unilateral adrenal carcinoma			+ to +++	+++		
Adrenogenital syndrome	1. Bilat. adrenal hyperplasia	a. Congenital	Nonsalt loser	+++	− or N	N	+
			Salt loser	+++		—	
			Hypertension	+++		+ (as DOC)	
		b. Acquired		+++		N	
	2. Virilizing adrenal tumor			+++	N	N	+
Feminizing tumor	Adrenal tumor			N	N	N	+++
Primary hyperaldosteronism	Adrenal tumor			N	N	+ to +++	N

noma, control values may be elevated, but usually no response to ACTH occurs. On the other hand, in bilateral adrenal hyperplasia or in unilateral adrenal adenoma a hyperresponse is often seen.[38]

Urinary Corticosteroids

METHODS OF ASSAY. With the technique of Glenn and Nelson,[26] after enzyme hydrolysis, the steroids are extracted by chloroform; the extract is then washed with tenth-normal sodium hydroxide solution, and chromatographed on a florisil column. The Porter-Silber reaction is then carried out on the residue.

The method of Reddy, Jenkins and Thorn[57] does not use column chromatography.

Sodium bismuthate oxidation by the method of Norymberski[53] transforms the 17-hydroxycorticoids into 17-ketosteroids, which are then measured by the Zimmermann reaction.

SIGNIFICANCE. The group of steroids measured by the first two methods represents approximately one third of the end products of the metabolism of cortisol. The method of Norymberski will also measure the 20-hydroxylated metabolites of cortisol (17-ketogenic steroids).

NORMAL VALUES. With the method of Glenn-Nelson, the range for male adults is 3 to 10 mg. per 24 hours., and 2 to 8 mg. for female adults.

ABNORMAL VALUES. (See also Plasma 17-OH-CS.) In inanition states

and anorexia nervosa the urinary corticosteroids are decreased, but plasma levels are normal. Immediately before death the urinary values are normal or low, while the concentrations in plasma are markedly increased. This has been shown to be failure of liver function.[62]

REMARKS. The relative merits of blood and urinary corticosteroids have been discussed extensively. It is our feeling that the information obtained from these two assays is quite different: the urinary corticosteroids give some idea of the total daily production, while the blood corticosteroids indicate the level of circulating 17-OH-CS at a specific time.

Total Urinary 17-Ketosteroids (17-KS)

METHOD OF ASSAY. Various modifications of the original method of Callow, Callow and Emmens[9] are used for the preparation of urinary extracts. Acid hydrolysis of the conjugated compounds is carried out, and the free steroids are extracted by organic solvents. The extract is washed with 10 per cent sodium hydroxide and water, and the Zimmermann reaction is applied. (An ethanol solution of 17-KS, in the presence of 1.2 per cent ethanol solution of meta-dinitrobenzene and 20 per cent ethanol solution of potassium hydroxide, gives a purple color with a maximum absorption at 520 millimicrons.)

SIGNIFICANCE. Androgens are excreted in urine either as 17-ketosteroids or as 17-hydroxy-steroids. For example, only 25 to 30 per cent of an administered dose of testosterone is excreted as 17-KS in the urine. Consequently the urinary 17-KS values represent only a part of the total production of androgen.

NORMAL VALUES. During the first few weeks of life the daily excretion of 17-KS may be as high as 2 mg., after which the values fall to 0.5 mg. or less.[77] Between the ages of six and eight years the levels are usually 0.5 to 1 mg., but undergo a progressive rise during puberty to reach adult levels by the age of 18 to 20 years.

ABNORMAL VALUES. The levels are decreased in cases of adrenal insufficiency, but this decrease is usually not as marked as that observed for 17-hydroxycorticosteroids.

Table 10 shows the conditions under which urinary 17-KS values are increased.

In children ACTH administration does not usually cause as great an increase in 17-KS as it does in adults. Cortisone administration in proper dosage may differentiate adrenogenital syndrome due to a virilizing adrenal tumor from that due to congenital adrenal hyperplasia. In the latter case urinary 17-KS may be expected to return promptly to normal,[76] while they do not in cases of adrenal tumor.[25]

Fractionation of Urinary 17-Ketosteroids

When the daily excretion of 17-KS is increased, it is often important to study their pattern in detail. Various modifications[36] of the original method of Dingemanse et al.[19] are used for this purpose.

A rough idea of the pattern of 17-KS may be obtained by less complicated but also less specific techniques. The method of Allen, Hayward and Pinto[4] detects the presence of large amounts of dehydroepiandrosterone; if this compound represents more than 50 per cent of the total 17-KS value, the presence of a virilizing adrenal tumor is strongly suggested.

Blood 17-Ketosteroids

The present methods are rather complicated,[24, 45] and the significance of blood androgens is not yet clear.[46]

Electrolyte-Regulating Factor (Aldosterone)

It is evident that the study of serum electrolytes, as well as sweat and saliva sodium-potassium ratios, is of great importance in the diagnosis of syndromes involving disturbance of the electrolyte-regulating factor. The Robinson-Power-Kepler water test may also be of value.[58]

In recent years bioassays have been devised for the measurement of sodium-retaining hormones.[68, 70] Urinary extracts are administered to adrenalectomized rats, and their effect on sodium, radio-sodium or sodium-potassium excretion in the urine is compared with that obtained by the administration of known amounts of DOCA.

Elucidation of the chemical structure of aldosterone[69] has permitted the development of chemical methods which utilize paper and column chromatography of the urinary extracts for isolation of the steroids.

Luetscher et al.[39] and many other investigators have reported an increased sodium-retaining activity in the urine of patients with nephrosis, heart failure with edema, and other conditions with low serum sodium. The syndrome of primary hyperaldosteronism has been described by Conn.[14]

Estrogens

Estrogen excretion is increased in some cases of hyperadrenocorticism (see Table 11). In the adrenogenital syndrome it is not clear whether estrogens are produced by the adrenal per se or whether they are metabolites of the androgens which are secreted in large amounts. In

feminizing adrenal tumors, however, estrogens are probably produced in excess.

Techniques for estrogen determination will be discussed under Gonadal Hormones.

Progestins

It has been shown that in the adrenogenital syndrome due to congenital adrenal hyperplasia there is a definite increase in the excretion of pregnanetriol. The adrenal precursor of this steroid is thought to be 17-hydroxy-progesterone. Bongiovanni and Clayton[6] described a method for the separation and measurement of pregnanediol and pregnanetriol in urine which may be helpful in the differential diagnosis of hyperadrenocorticism.

ADRENAL MEDULLA

The existence of a functionally active pheochromocytoma as a cause of paroxysmal or sustained hypertension in children may be directly confirmed by the demonstration of increased quantities of norepinephrine and epinephrine in the urine. In many cases the diagnosis may be made indirectly by the use of response tests based on the action of epinephrine and norepinephrine blocking agents.

Catechol Amines

Pressor amines may be determined quantitatively in urine by the use of a bioassay procedure after aluminum hydroxide adsorption.[23] A highly increased excretion of norepinephrine and, in some cases, epinephrine establishes the presence of a functionally active pheochromocytoma. A comprehensive review of the available techniques using bioassay, paper chromatography, photofluorometry and absolute chemical quantitation of norepinephrine and epinephrine has been published recently by Goldenberg et al.[27]

Regitine Test

Adrenolytic agents such as dibenamine, benzodioxane and phentolamine hydrochloride (Regitine) block the pressor effects of circulating catechol amines, thereby producing a fall in blood pressure. Regitine seems better adapted to pediatric use since it may be administered orally, intramuscularly or intravenously, and because its hypotensive effect is more prolonged. Side effects with this preparation are rare. The dose is usually 1.0 to 2.5 mg. intramuscularly, or 25 mg. orally.[15]

Equivocal results are sometimes obtained in children, and for this reason direct measurement of pressor substances is by far the better diagnostic test.[13]

Persistent rather than paroxysmal hypertension is a much more common manifestation of this condition in children. The histamine test, which may be of diagnostic importance in the adult paroxysmal type, is seldom of value in pediatric patients.

Hyperglycemia and glycosuria are also more commonly seen in adults with pheochromocytoma because of a generally higher production of epinephrine by these tumors; however, in children and adults norepinephrine is the predominant secretion.

GONADAL HORMONES

The principal androgens produced by the human testis seem to be testosterone and $\triangle^4$-androstenedione, but only part of these compounds is excreted in the urine as steroids with a 17-ketone group (17-KS). It is generally agreed that testicular 17-KS represent approximately one third of the total urinary 17-KS in the male. The testis also produces estrogens, but both androgenic and estrogenic steroids are secreted mainly after puberal maturation of the gland.

Under the influence of pituitary tropic hormones the matured ovary produces estrogens and progesterone. There is also the possibility that androgens are secreted by this gland.

Tests for Androgens

Chemical techniques for the determination of 17-KS have been discussed under Hormones of the Adrenal Cortex. For the most part, they have replaced bioassays for androgens.

An increase in gonadal androgens is seen in cases of Leydig cell tumor of the testis and in cases of virilizing ovarian tumors (see Table 12). In cases of so-called constitutional sexual precocity the urinary 17-KS may be slightly above the normal average.

Tests for Progesterone

The study of progesterone activity is rarely indicated in infants and children. It may be of some value, however, in cases of sexual precocity or irregular menstruation. The bioassay of Hooker-Forbes[32] and the recent chemical methods for the determination of progesterone in blood are complicated techniques. Usually the clinical tests—basal temperature, vaginal smear and endometrial biopsy—will determine whether progesterone is being secreted normally by the corpus luteum.

TABLE 12. *Hormonal Disturbances in Sexual Precocity*

TYPE	CAUSE	BREAST DEVELOPMENT	VAGINAL ESTRINIZATION	MENSTRUATION	OVULATION	PUBIC HAIR GROWTH	CLITORAL HYPERTROPHY, HIRSUTISM	URINARY EXCRETION		
								17-KS*	GONADOTROPIN BIOASSAY	ESTROGENS*
Isosexual	*Idiopathic* "Constitutional type"	+	+	+	+	+	0	2	+ or 0	2
	Premature pubarche	0	0	0	0	+	0	1–2	0	1
	Premature thelarche	+	0	0	0	0	0	1	0	1
	Intracranial lesions Congenital defects Neoplasms, hamartomas Encephalitis Fibrous dysplasia of bone	+	+	+	+	+	0	2	+ or 0	2
	Ovarian lesions Granulosa cell tumor	+	+	+	0	+	0	1	0	2
	Chorioepithelioma	+	+	+	0	+	0	1	+	2(?)
	Teratoma	+	+	+	0	+	0	1	+ or 0	2(?)
	Medicational (estrogen)	+	+	?	0	0	0	1	0	3–4
Masculinizing	*Adrenal lesions* Adrenogenital syndrome Adrenal hyperplasia Virilizing adrenal tumor	0	0	0	0	+	+	3–4	0	3–4
	Cushing's syndrome Hyperplasia Tumor	0	0	0	0	+	+	1–4	0	1–3
	Ovarian lesions Arrhenoblastoma Adrenal rest tumor	0	0	0	0	+	+	1–3	0	1

1. Normal for age.
2. Adolescent level.
3-4. Marked elevations.

Tests for Estrogens

In female infants or children the best and simplest test for estrogenic activity is the study of the vaginal smear, using the special stain devised by Shore.[66] Pink cells with pyknotic nuclei are typical of full estrinization. Bioassays using as an end-organ the vaginal smear of castrated mice[3] or the uterine weight of immature mice or rats[37] are also available.

In the chemical determination of urinary estrogens the Kober reaction or fluorescence reactions are used for quantitative estimation. Because

of the different potencies of the various estrogens occurring in human urine, when one uses either bioassay or chemical techniques, it is necessary to separate the individual compounds by column or paper chromatography, or counter current distribution and measure them separately.

Buccal Smear for Chromosomal Sex

Simplified methods for the determination of the nuclear sex chromatin pattern using smears from the buccal mucosa have been described by Barr and his associates[49] and by Nelson and his group.[44] This test has proved to be of great value in the diagnosis of gonadal dysgenesis and in the classification of pseudohermaphroditism. The finding of a male chromatin pattern in a patient suspected of gonadal aplasia (80 per cent of cases) who has not yet reached an age when gonadotropins are detectable would establish the diagnosis, but a female pattern would not exclude it.[30] At least two thirds of the patients with Klinefelter's syndrome show a female sex chromatin pattern. The test is frequently of value also in differentiating female pseudohermaphroditism with congenital adrenal hyperplasia from cases of male pseudohermaphroditism; female pseudohermaphroditism *without* congenital adrenal hyperplasia is a rather rare condition.

THYROID HORMONES

Roche and Michel reviewed the problem of the synthesis of thyroid hormones and the nature of the circulating compounds.[59] Thyroxin and small amounts of 3,5,3′-triiodothyronine and 3,3′-diiodothyronine appear to be the main circulating thyroid hormones in man.

No single sign or test is sufficient to determine the thyroid status of a patient, and the entire clinical and chemical picture must be evaluated. The clinical signs are of the greatest importance; these are, mainly, the functional changes (circulatory signs, muscle tone, degree of sweating, intestinal activity), the study of growth and development (height age, bone age, dental development, skeletal proportions, and the like), the state of skin and hair, and the mental development.

A certain number of tests may often be useful: the basal metabolic rate, the serum cholesterol, the protein-bound iodine and butanol-extractable iodine, and studies with radioactive iodine.

Basal Metabolic Rate (BMR)

This test is quite reliable in adult patients, but with the usual techniques is unsatisfactory in children.

Serum Cholesterol

The serum cholesterol is markedly increased in the majority of cases of hypothyroidism (300 to 600 mg. per 100 ml.), except in children under two years of age, in whom the levels may not exceed the upper limits of the normal range.

Protein-Bound Iodine (PBI) and Butanol-Extractable Iodine (BEI)

Circulating thyroid hormones are bound to protein, and the PBI is used as an index of their levels. Remember, however, that nonspecific iodinated proteins are also measured by this method. The BEI determination is somewhat more specific and, contrary to the PBI, is not influenced by exogenous iodine (pyelography, bronchography, iodinated medications, and so on).

Normal values are as follows:

	PBI (micrograms %) (Danowski et al.[18])	BEI (micrograms %) (Man et al.[43])
At birth	6.0–10.7	4.3– 7.1
1st week	9.0–14.0	7.0–11.7
1 week to 3 mos.	5.6– 9.2	4.6– 8.0
3 mos. to 1 yr.	5.3– 7.3	4.6– 8.0
Adults	3.5– 8.0	3.3– 7.3

The BEI is usually 0.5 microgram per 100 ml. lower than the PBI, but in some goitrous cretins the difference may be greater.

These tests are of considerable diagnostic value and are also useful as guides to therapy in both hyperthyroidism and hypothyroidism.

In hypothyroidism under desiccated thyroid therapy, euthyroidism is attained when PBI levels are restored to normal, while levels between 10 and 14 micrograms must be obtained with thyroxin therapy; on the other hand, the triiodothyronine dosage required for clinical euthyroidism produces PBI concentrations slightly lower than normal.

Studies with Radioactive Iodine

I^{131} uptake by the gland will indicate the ability of the thyroid to trap iodine. It is characteristically decreased or nil in athyreotic patients and is increased in hyperthyroidism. The uptake is also increased in cases of endemic cretinism due to lack of iodine intake and in goitrous cretins, in whom Stanbury et al.[71] have shown the inability of the gland to convert inorganic iodine into thyroxin. This problem has been discussed in greater detail in another clinic of this volume (Goitrous Hypothyroidism, p. 849). When the I^{131} uptake is decreased, the administration of TSH will restore the uptake to normal in cases of hypo-

thyroidism due to hypopituitarism, while it will not in cases of primary hypothyroidism.[56] The results obtained from such a test must be critically evaluated, however. Iodinated medication given before the I^{131} test will invalidate the results.

Our present knowledge would indicate that even though the amount of radiation received by the child from a test dose of I^{131} is harmless, it might be better to carry out the test only when it is essential to the diagnosis.

PARATHYROID HORMONE

The diagnosis of primary parathyroid dysfunction may be made only upon the demonstration of altered calcium and phosphorus metabolism. Table 13 gives a general classification of the causes of hypercalcemia and hypocalcemia encountered clinically.

TABLE 13. *Disorders Causing Hypocalcemia and Hypercalcemia*

	SERUM			URINE		
	Ca	P	Alk. Phos.	Ca	P	Ca Retention
Primary hyperparathyroidism	+++	−−	++	+++	++	−−
Acute disuse osseous atrophy	++ or N	N	N	++	N	−
Destructive osseous neoplasia	++ or N	N	N	+	N	− or N
Vitamin D intoxication	+++	N or +	N	+	N	N + or −
Infantile idiopathic hypercalcemia	+++	N or +	N	+	N	N + or −
"Milk and alkali" hypercalcemia	++	N or +	N	± N	N	N or +
Carcinoma and sarcoid without osseous involvement	++	N	N	N	N	N
Hyperproteinemias	Tot. ++ Ion, N	N	N	N	N	N
Hypoparathyroidism	−−−	+++	N	−−	−−	+ or N
Pseudohypoparathyroidism	−−−	+++	N	−−	−−	+ or N
Glomerular insufficiency, secondary hyperparathyroidism	−−	+++	++	−−	−−	−
Infantile rickets with tetany	−−	−−−	+ or ++	−−	− or N	− or N
Steatorrhea with rickets	−− or N	−−−	+	−−	− or N	− or N
Renal tubular defects (renal acidosis)	−− or N	−−−	+	− or +	++	− or N
Postacidotic hypocalcemia	−−	−−	N	−−	−	+
Rickets with hypophosphatasia	N	N	−−	N	N	− or N
Hypoproteinemias (nephrosis, etc.)	Tot. −− Ion, N	N	N	N	N	N
Neonatal tetany	−−	++	N			

Modified after Wilkins.[75]

Primary hyperparathyroidism is characteristically associated with hypercalcemia, hypophosphatemia, hyperphosphatasia, hypercalcuria and a negative calcium balance on a normal or low calcium intake. In mild hyperparathyroidism there is frequently no osseous involvement, in which case alkaline phosphatase values are within the normal range. Measurement of the percentage of renal phosphorus reabsorption may be of additional diagnostic aid in questionable cases.[64] Hypercalcemia and hypophosphatemia may be unimpressive in some cases in which parathyroid adenomas are subsequently proved, and it has been shown recently that borderline chemistries warrant a more thorough evaluation.[5]

Primary hypoparathyroidism may be confirmed by correction of the hypocalcemia and hyperphosphatemia on the administration of parathyroid hormone, A.T. 10 or large doses of vitamin D. The chemical abnormalities encountered in pseudohypoparathyroidism, on the other hand, are not altered significantly by parathyroid hormone, but do respond to A.T. 10 and large doses of vitamin D. A modification of the Ellsworth-Howard test[22] suitable for children may be performed by administering 50 to 250 units of parathyroid hormone every six hours over a four-day period. In true primary hypoparathyroidism a definite decline in the serum phosphorus level is observed, while little or no response occurs in pseudohypoparathyroidism.

HORMONES OF THE PANCREAS

The integral relationships between the endocrine pancreas and the internal secretions of other organs are well recognized, though they are but partially understood. Basically, the blood glucose level is governed by the productive activity of the beta-cell (insulin), actively balanced against a combination of contra-insular factors of pituitary, adrenal, pancreatic (? alpha-cell), hepatic and dietary origin. The absence of one or several contra-insular factors, or the excessive secretion of insulin, may result in blood glucose depletion; the hypoglycemic state may therefore be considered to be the result of relative or absolute hyperinsulinism.

Fasting Blood Glucose

The concentrations of *true* blood glucose[52] after a 12- to 14-hour fast should confirm the presence of hypoglycemia and at the same time tend to rule out postprandial "insulin sensitivity" (functional hypoglycemia) as a diagnosis. True blood glucose levels below 50 mg. per 100 ml. may be considered to be hypoglycemic after the neonatal period, and such concentrations in the presence of ketonuria would favor a

diagnosis of hepatic glycogen storage disease. Concentrations exceeding 200 mg. per 100 ml. in patients with glycosuria and ketonuria establish the diagnosis of diabetes mellitus with reasonable certainty.

Tolerance Tests

The following response tests may be used in the evaluation of hypoglycemia in childhood. The diagnostic process is time-consuming, an interval of three to five days being required after each procedure. It is of the utmost importance that before *each* test the patient be fed a diet in which at least 50 per cent of the caloric content is carbohydrate and less than 35 per cent is fat.

Intravenous Glucose Tolerance Test. After a 12-hour fast 0.7 gm. of glucose per kilogram of body weight is administered intravenously at a constant rate over a 30-minute period. (This may be given as a 5, 10 or 20 per cent solution, and when possible the volume should be between 50 and 75 ml.). Blood samples for true glucose determination are obtained before infusion and one-quarter, one-half, one, two, three, four and five hours afterwards.

Normally, the blood glucose falls from hyperglycemic levels to control values in about two hours. Continued insulin secretion then causes a further slight decrease in the normal person, but contra-insular factors are responsible for a return to levels above the initial base-line by the third hour. A deficiency in any of these hyperglycemic factors tends to allow the glucose to fall to hypoglycemic levels within three to five hours, where it may remain for varying periods and during which time there may be clinical symptoms. Functional or postprandial hypoglycemics may react in this fashion, but usually there is a return to normoglycemia by the fourth hour. A prolonged hypoglycemic response to the test may be seen in primary or secondary hypoadrenocorticism; definitive diagnosis should rest upon the demonstration of decreased plasma 17-OH-CS levels. In hepatic disease (e.g., glycogen storage disease) the induced rise in blood glucose is sustained longer than in the normal and in severe cases may resemble a diabetic response. Pancreatic islet cell tumors, unfortunately, respond erratically to this procedure, and the curves obtained may be flat, normal or even diabetic in configuration.

In the diagnosis or evaluation of therapy of diabetes mellitus in children the glucose tolerance test has little to offer over fasting and postprandial blood sugar determinations. The test may be of value in questionable cases, however.

Epinephrine and Glucagon Tolerance Tests. To determine the existence of adequate hepatic glycogen stores and as a test of glycogenolytic function in hypoglycemia, the response of blood glucose con-

centration to the administration of epinephrine or glucagon is studied. After the usual three to five days on a high carbohydrate diet, and after a 12-hour fast, 0.01 ml. of 1:1000 epinephrine per kilogram of body weight is injected subcutaneously. Blood glucose determinations are then performed at 15, 30, 45, 60 and 90 minutes. The response to glucagon is measured in an identical fashion after the subcutaneous or intravenous administration of 0.02 ml. (20 micrograms) of glucagon per kilogram of body weight.

A rise in blood glucose of more than 20 mg. per 100 ml. with either of these tests is evidence of normal glycogenolysis, while a lack of response would indicate hepatic glycogen depletion or an inability to mobilize liver glycogen (e.g., glycogen storage disease). However, a normal response to either glucagon or epinephrine does not definitely rule out hepatic disease as a cause of hypoglycemia.[10] Both epinephrine and glucagon (hyperglycemic-glycogenolytic factor) activate phosphorylase and accelerate the reaction from glycogen to glucose-1-phosphate.[73] Glucagon, however, appears to act only on hepatic phosphorylase, while epinephrine affects both liver and muscle.

Intravenous Glucose Tolerance Test After ACTH. The syndrome of idiopathic infantile spontaneously occurring hypoglycemia, described by McQuarrie,[42] characteristically shows a favorable clinical response to ACTH. Correction of an abnormal intravenous glucose tolerance curve after the administration of ACTH in therapeutic doses is compatible with such a diagnosis. Before repeating the tolerance test, plain ACTH is given intramuscularly over a four-day period in the amount of 4 mg. per kilogram of body weight per day divided into four equal doses given every six hours. In many cases a more practical procedure is the determination of a fasting blood glucose curve during prolonged ACTH therapy. The test is somewhat nonspecific in that the hypoglycemia associated with anterior pituitary insufficiency may give a similar response and patients with islet cell tumors have been known to improve on prolonged corticotropin therapy.[42]

In some cases of spontaneous idiopathic hypoglycemia a fall in the fasting true blood glucose is precipitated by the administration of certain amino acids.[12] This entity may be differentiated by feeding a test dose of casein (1.5 gm. per kilogram) to the fasting patient and determining the blood glucose concentration at frequent intervals during the next two hours.

Blood Glucose after Prolonged Fasting

Hypoglycemic attacks in the presence of normal responses to the above-mentioned tests would indicate the possibility of an islet cell tumor. Under these circumstances a 24-hour fast is warranted, and when

such tumors are present, hypoglycemia with the clinical picture of an attack may be anticipated. The test is often used as an indication for laparotomy.

Other Tests

Insulin tolerance tests are not without danger in children with hypoglycemia and are of little value when that condition is already known to exist. As a test of responsiveness or resistance to insulin in patients with a diabetic type of glucose tolerance curve, the "glucose plus insulin test" is sometimes indicated. A standard oral glucose tolerance test is repeated and 0.25 unit of regular insulin per kilogram is injected subcutaneously exactly 10 minutes after the glucose has been given. In the normal person, after 60 minutes, the two curves show a difference of 30 to 55 mg. per 100 ml. Failure of insulin to lower the curve suggests insensitivity to insulin, as is sometimes seen in acromegaly or Cushing's syndrome. In some other cases, the cause of "insulin-resistant diabetes" is obscure.

Galactosemia as a cause for hypoglycemic attacks may be ruled out in the absence of galactosuria. Precipitous falls in blood glucose may occur during a galactose tolerance test so that the diagnosis should be made by other means whenever possible.[35]

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FOREWORD

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Consulting Editor

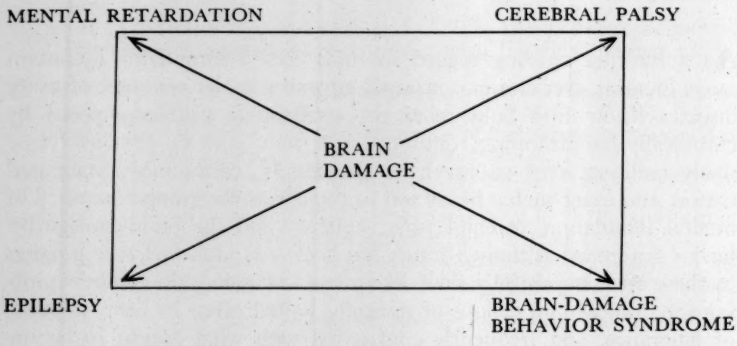
As a traveller crossing rugged foothills sees a formidable mountain range looming ever clearer, our rapid advances in the conquest of acute diseases throw into bold relief the challenging problems posed by chronically handicapping conditions. Of these entities, few involve so many children, cost so much to the family, community, state and nation, and exact such a heavy toll of tragedy as the group composed of mental retardation, cerebral palsy, epilepsy and the brain-damage behavior syndrome. Although much has been accomplished, our progress in these areas is painfully slow, like a team of mountain climbers probing sometimes-blind canons of research, halted often by deep crevasses of ignorance, and frequently confronted with what appear to be impassable barriers.

Fortunately, pediatrics, like the very children it treats, is characterized by energy, optimism and adaptability. Having solved many of our important, but simpler, problems dealing with the acute diseases, we are now devoting increasing effort to unraveling the mysteries of the more complex chronic conditions. Thus on every hand we see research in diseases of the central nervous system burgeoning, the laudable growth of teamwork and group approach of many disciplines in the management of these conditions, greater indoctrination of physicians in their importance, and steady growth of community and statewide programs for the neurologically handicapped child.

For these reasons it was considered appropriate to publish herein a Symposium on Brain Damage in Children, defining brain damage as any acquired injury of a previously normal human brain. Such injuries may occur prenatally, perinatally or postnatally. Emphasis is given to what is known about potential avoidance of brain damage, since the ultimate objective is prevention.

When a child suffers brain damage, one of three things may occur:

(1) full recovery; (2) death; (3) residual disability. Our concern here is with the residual disabilities that may occur. The four principal ones are (1) mental retardation; (2) cerebral palsy; (3) organic epilepsy; (4) the brain-damage behavior syndrome. A child who has suffered brain damage may have any one, or combinations, of these disabilities. When we observe a child with one of these conditions, we should screen for the other entities. Only in this way can comprehensive evaluation and total management be achieved. This situation may be represented in the following diagram, in which each of the four principal residual disabilities occupies one corner of what might be called the "brain damage rectangle." Isolated neurologic defects unaccompanied by one of the four principal disabilities may also exist.



It would be naive to suppose that in a symposium of this length and limited to these subjects we might present a comprehensive picture of all problems associated with these conditions. That is not our objective. We only seek to give the reader some of the current concepts of progress in these fields. By doing this, we hope to stimulate a greater interest in these entities which often represent to the pediatrician and general practitioner complex and baffling problems, and to the patient and the family psychologic, economic and medical millstones.

In conclusion, I wish to thank all the contributors to this symposium who have given of their time and talent in the preparation of these papers.

EXPERIMENTAL TERATOLOGY

With Special Reference to Congenital Malformations of the Central Nervous System

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HAROLD KALTER, PH.D.

JEAN F. GEIGER, B.S.

In recent years several methods have been developed which permit experimental production of congenital malformations of the central nervous system in mammals. Such experiments should be of interest to pediatricians since some of the induced anomalies resemble human malformations.

In general, however, the experimental conditions resulting in the birth of malformed young do not simulate environmental conditions in man. The experimenter subjects the pregnant animals to a set of circumstances, usually very artificial, to obtain a high percentage of abnormal young which can be studied embryologically and morphologically. It should be obvious, therefore, that the fact that a certain malformation can be produced by a certain experimental arrangement does not prove that such malformations in man are the result of similar circumstances. Experiments of this type can often be of value, however, by demonstrating the morphogenetic processes which lead to mal-

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formations. Many hypotheses or speculations about the formation of congenital defects can now be subjected to experimental proof.

Radiation has been used as a teratogenic agent for several decades. In 1922 Bagg[2] found that treatment of pregnant rats with gamma radiation towards the end of pregnancy resulted in the birth of young that developed atrophy of the cerebral cortex and defects of the eyes and other organs. Congenital hydrocephalus was first produced by x-rays by Nobele and Lams in 1927.[46] It was not till 1935, however, when Job et al.[30] reported their results on x-ray-induced hydrocephalus, that the method of x-ray teratogenesis was first shown to be a useful instrument of developmental analysis. The importance of the work of Job

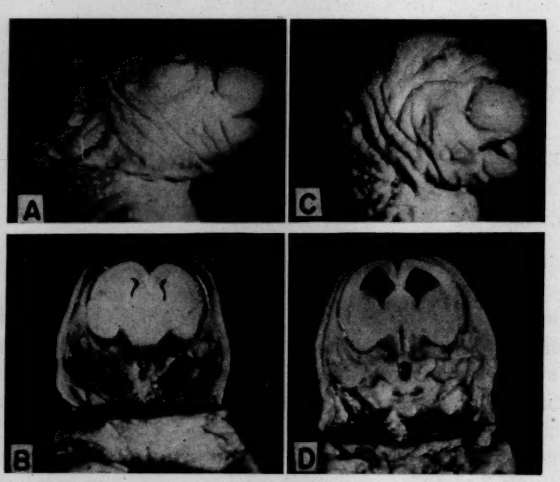

Fig. 46. *A*, External appearance of head of a newborn control rat. *B*, Frontal section through this head. *C*, External view of newborn rat with hydrocephalus produced by x-irradiation. *D*, Frontal section through this head showing enlargement of lateral ventricles.

et al. lies in their having treated animals at specific times during gestation, which thus enabled them to determine periods of susceptibility to various malformations.

Kaven, two years later,[31, 32] introduced the additional refinement of using genetically homogeneous animals. In this material a hydrocephalus was induced that became apparent a few days after birth. More recently, x-ray-induced congenital hydrocephalus has been reported by Russell,[53, 54] Wilson et al.[71] and Hicks.[26] Figure 46, *C*, shows an animal with hydrocephalus, and Figure 46, *D*, a section through the head of the same animal. This specimen was obtained in our laboratory by irradiation of the mother on the tenth day of gestation.

Another malformation produced in the offspring of x-irradiated pregnant animals is exencephaly. In Kaven's material [31, 32] this malformation took two forms, a less extreme anomaly appearing relatively late in prenatal development, and a more extreme condition appearing earlier, the animal never surviving to birth. Exencephaly (Fig. 48) was frequently produced by Warkany and Schraffenberger[67] and by Hicks.[26] In Russell's work[53, 54] "cranial blisters" were observed which could have been small, skin-covered encephaloceles; and Wilson et al.,[71] examining young fetuses several days after treatment, found ruptured brain tissue, the further development of which would very likely have led to exencephaly. Microcephaly was induced in the offspring of irradiated animals by Kosaka.[33] This finding is of interest, since microcephaly has often

Fig. 47. On the left a newborn control rat. The other specimens show exencephaly and other head malformations produced by x-irradiation.

been observed in children whose mothers were exposed to large doses of x-rays.[41] Russell[53, 54] has succeeded in producing spina bifida by x-rays, and a preliminary analysis[1] has been published of the development of this anomaly.

The design of most of these x-ray studies has been to examine the effects of irradiating at either a few or many developmental stages with the purpose of defining precisely the malformations observable at a particular time with varying doses of x-rays. Another approach has been to follow the morphogenesis of a malformation in the attempt to discover the earliest observable cellular or histological deviation to which the malformation may ultimately be referable. Hicks[26] surveyed the effects on the central nervous system of treatment with x-rays at many

stages of embryogenesis. His work well illustrates the changes in radiosensitivity that occur with advancing development. He found that the neuroblast is the cellular element most susceptible to destruction by ionizing radiation, and that destruction of this cell type causes a variety of malformations of the brain, the pattern changing with the time of treatment.

Feeding pregnant animals diets lacking single vitamins, with or without an added vitamin antagonist, has been a much-used teratogenic method. Deficiency of any one of several B vitamins has been noted to produce congenital malformations of the central nervous system in the offspring of treated animals. Richardson and Hogan[48] reported that mothers fed a diet containing vitamins A and D and all the then known water-soluble vitamins except folic acid, had a small percentage of offspring that developed hydrocephalus not earlier than 10 days of age; and in a later experiment Richardson and DeMottier, using animals of different stock,[49] observed congenital hydrocephalus after the same treatment. Subsequently it was found possible to increase the frequency of the anomaly greatly by adding a folic acid antagonist to the deficient diet.[27] A deficiency of vitamin B_{12} may also have some significance in the development of the defect,[47] which is prevented by the addition of this vitamin to the diet.[20, 47]

Refinements in the technique of inducing malformations by folic acid antagonists were introduced by Nelson et al.,[44] who by these methods were able to produce high frequencies of a large diversity of malformations. It has been possible for these investigators to produce hydrocephalus in the offspring of pregnant animals that were fed an antagonist for as short a time as 36 hours.[45]

Another folic acid antagonist induced hydrocephalus in animals[55, 58] and in man.[57, 59] Thiersch[57, 59] gave 6 to 12 mg. of Aminopterin, a powerful folic acid antagonist, orally to 24 pregnant women during the first trimester in attempts to produce therapeutic abortion. In four cases the fetuses showed malformations such as anencephalus, hydrocephalus, meningoencephalocele or cleft lip and palate. It is of interest that all four of these anomalies have been induced by folic acid antagonists in experimental animals.

A chronic deficiency of riboflavin produced by feeding a riboflavin-deficient diet over a relatively long period of time has been found to induce predominantly skeletal defects.[66] However, when an acute riboflavin deficiency is produced by use of a riboflavin antagonist, congenital hydrocephalus occurs[43] in addition to many other congenital malformations. The use of this antagonist has been extended in our laboratory to strains of inbred animals. The offspring of some strains have been found to have severe cerebral malformations (Fig. 48) after such treatment. The anomaly in these animals consists in a large internal hydro-

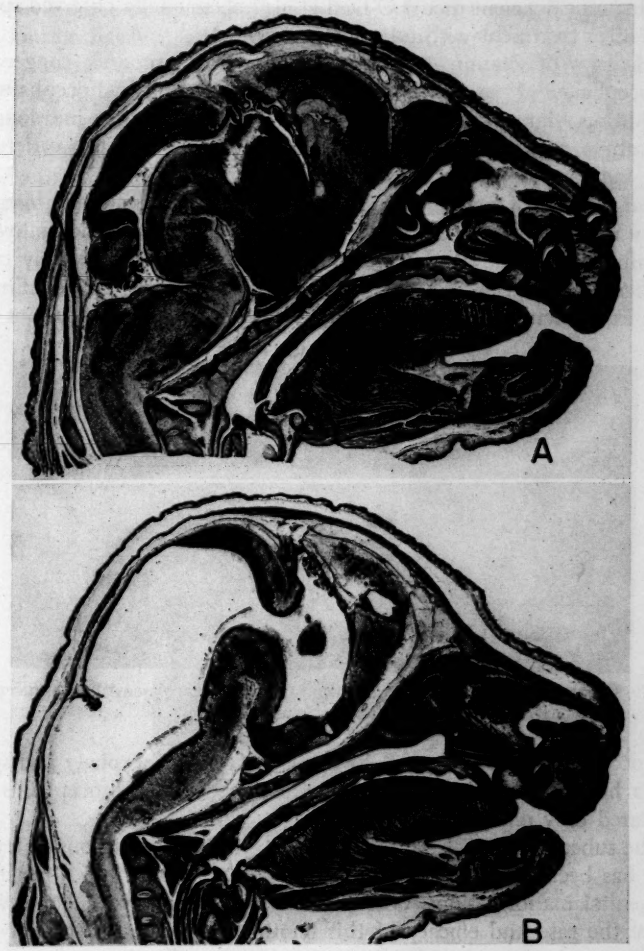

Fig. 48. Sagittal sections through the heads of newborn mice. A, Control. B, Marked enlargement of third and fourth ventricles induced by the use of a riboflavin antagonist.

cephalus, including a cystic fourth ventricle, and extreme thinning of the cortex and absence of the cerebellum.

Hydrocephalus is not the only congenital malformation of the central nervous system that can be produced by vitamin B deficiencies. Exencephaly has frequently been the result of treatment following pantothenic acid-deficient diets,[3, 9, 34, 72] folic acid-deficient diet[14, 15, 16, 44, 45, 47, 57, 58]

and thiamine-deficient diet.[69] O'Dell et al.[47] occasionally observed spina bifida after treatment with folic acid antagonist.

Deficiency of vitamin A has also been noted to produce congenital hydrocephalus[37, 50] as well as postnatally developing hydrocephalus.[36] In addition, vitamin E deficiency[4, 63] has been found to be injurious to the embryo, and hydrocephalus and exencephaly, as well as a variety of other malformations, have been observed as a result.

A large excess of vitamin A fed to pregnant animals is also teratogenic. This was discovered by Cohlan,[6, 7] who found that by this means hydrocephalus, exencephaly and spina bifida were induced in relatively large numbers of offspring. Giroud and Martinet[17, 18] generally confirmed these experiments, and produced exencephaly and spina bifida, but not

Fig. 49. On the left a newborn control mouse. The other specimens show exencephaly induced by trypan blue injections

hydrocephalus, by this means. In our laboratory exencephaly and spina bifida have also resulted from such treatment, but hydrocephalus has appeared only rarely.

The subcutaneous injection of females with dilute solutions of trypan blue has been found to be a fruitful method of producing a variety of congenital malformations. Gillman et al.[12, 13] were the first to demonstrate the ease and efficacy of this teratogenic method. Especially frequent among the anomalies appearing in the offspring was a hydrocephalus marked by a completely communicating ventricular system. Wilson[70] also obtained hydrocephalus with trypan blue, but the malformation in this experiment was accompanied by an aqueduct that was obliterated or reduced in caliber. Treatment with trypan blue by many other investigators has also resulted in hydrocephalus.[10, 11, 35, 38, 39, 40, 70] Exencephaly and spina bifida (Figs. 49, 50) were observed by many workers after trypan blue.[12, 13, 21, 22, 35, 38, 39, 40, 68] In addition, Gunberg[21, 22] noted the occurrence of an Arnold-Chiari-like malformation in the offspring of trypan blue-treated animals, which seems to be

causally related to spina bifida aperta produced by this method. This relationship has been confirmed in our laboratory.[68]

Several studies have been made of the effects of maternal trypan blue treatment on early fetal development. In this regard, Waddington and Carter[64, 65] and Hamburgh[23, 24] noted delay of closure of the neural folds of the head. In the material of these investigators this aberration was largely incompatible with fetal life, and except in a few instances of congenital exencephaly,[24] no abnormalities of the central nervous system were noted in newborn animals.

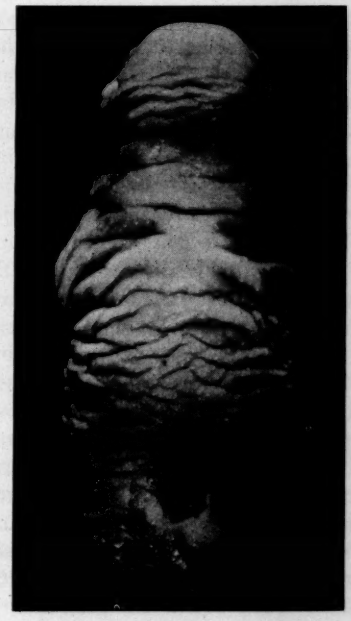

Fig. 50. Posterior aspect of newborn rat with spina bifida induced by trypan blue injections.

The methods mentioned so far are those most extensively used in teratologic studies. In addition to these, many other techniques have induced congenital malformations of the central nervous system. One is the method of subjecting pregnant animals at specific times during gestation to lowered atmospheric pressure. In three laboratories[8, 28, 29, 39, 40] exencephaly has resulted from this treatment.

Antagonists other than those of vitamins, which have been discussed above, have been noted to induce various cerebral anomalies. These include nucleic acid antagonists[62, 73] and amino acid antagonists.[60]

Certain antimetabolites used in cancer therapy have been shown to

induce exencephaly,[61] and nitrogen mustard, whose action is similar to that of these antimetabolites, has, when administered to pregnant animals, produced exencephaly in the offspring.[25, 42]

Interesting experiments were performed by Runner[51] and Runner and Miller,[52] who deprived pregnant animals of all food for 24 hours. By this method exencephaly was induced in significant numbers of the offspring. Perhaps similar to fasting in its metabolic consequences is insulin administration, which results in exencephalic offspring.[56] Animals of the same inbred strain were used in the fasting and insulin experiments. Another report of a brain defect, microcephaly, after insulin administration is by Chomette.[5]

A novel and apparently specific teratogenic method was discovered by Gluecksohn-Waelsch,[19] who injected an emulsion of brain tissue in females before conception and observed various abnormalities of the nervous system in young fetuses of these animals. Abnormalities did not occur after treatment with heart emulsion.

DISCUSSION

The production of congenital malformations of the central nervous system by subjecting pregnant animals to adverse environmental conditions represents a definite advance in the field of experimental neurology. Like other tools of experimental research, this line of investigation will prove fruitful only if used judiciously and if the results are interpreted in connection with experimental and clinical data obtained by other methods. It was pointed out in the introduction that none of the adverse conditions set in the experiments cited corresponds to conditions likely to occur in human pregnancies that result in congenital malformations. The teratogenic factors used in these experiments should, therefore, not be held responsible for similar malformations in children unless there is strong confirmatory evidence derived from observations in man.

It must be remembered that congenital malformations of the central nervous system sometimes occur spontaneously in animals, and that in many strains heredity can be clearly demonstrated. In other strains such "spontaneous" malformations occur less regularly, and, although heredity seems to play an important etiologic role, the mode of inheritance is not clearly understood. In such cases there also exists the possibility that nongenetic (environmental) factors contribute to the appearance of these anomalies. A third situation arises when malformations can be induced by experimental procedures in certain strains of animals, but not in others. This can be demonstrated by the use of inbred strains which show a differential response to identical environmental procedures. Finally there exist teratogenic methods of such

potency that they can induce malformations in nearly 100 per cent of the offspring irrespective of strain or species. Thus the experimental evidence available at present indicates that genetic as well as environmental factors may be responsible for congenital malformations of the central nervous system and that the respective role of these factors may be variable in different instances. This concept does not supply a simple formula for the explanation of such defects in man.

In the foregoing review effective teratogenic agents have been enumerated. It should be pointed out that their effectiveness depends upon dosage, timing, and susceptibility of the experimental animals, as well as upon their properties. Furthermore, it must be realized that malformations may vary in the different young of one litter, which indicates that intangible factors contribute to the expression of such anomalies. All these limiting conditions emphasize that generalizations should be avoided and that application of experimental results to human situations should be guarded.

Nevertheless such experiments can be of great interest to the clinician, since they permit following the development of congenital anomalies from their earliest appearance in the embryo to their final form in the newborn animal. Another field of application could be investigation of multiple anomalies of the central nervous system and observation of their mutual dependence or independence. For instance, the relation of spina bifida to hydrocephalus and the Arnold-Chiari malformation in man is a controversial subject. In such a controversy the experimental approach will probably be very fruitful.

The experiments cited have demonstrated that a clinical entity, such as hydrocephalus or spina bifida, may originate in differing ways. In some instances the investigation of the pathways leading to these anomalies in experimental animals may lead to a better understanding of the mechanisms involved in their formation in man. So far most of the work in this field has been done in small laboratory animals, but in recent years a trend toward the use of larger animals has been noted. If in the future larger animals with induced congenital malformations become available and a supply of material for experimental surgery is assured, new neurosurgical procedures and techniques may be developed with the help of such experimental material.

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THE CAUSES AND PREVENTION OF CEREBRAL PALSY

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The prevention of cerebral palsy and of other forms of neuropsychiatric impairment poses one of the great problems in present day medicine. Some half million of our children and youth are afflicted with cerebral palsy, with 10,000 new cases at birth every year; approximately 300,000 suffer from epilepsy; and no less than a million and a half are mentally retarded.[1] Not only are these children the cause of daily heartache to hundreds of thousands of parents, but they also impose an enormous burden on private, municipal, state and federal agencies. As pointed out by Cardwell, because of the chronicity of the disease, its many accompanying handicaps and the long duration of the rehabilitation process, services in such cases are prohibitively expensive except for the wealthy.[2] In New York State the care of a child with cerebral palsy in a hospital or residential home costs $4745 a year, and in a convalescent home, $2920 a year.[13] Moreover, VanMeter has pointed out that vocational rehabilitation of the adult cerebral palsied in the United States could stop a drain of half a billion dollars a year in the national economy.

Little's pioneer paper on cerebral palsy, published in 1861, was entitled "On the Influence of Abnormal Parturition, Difficult Labours, Premature Births, and Asphyxia Neonatorum on the Mental and Physical Condition of the Child, Especially in Relation to Deformities," a title which shows plainly enough that in the author's mind the condition was of obstetrical etiology.[8] Although medical opinion has receded from time to time from Little's position, present evidence indicates that, in the main, he was correct. This evidence is as follows:

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Among persons afflicted with cerebral palsy a history of premature birth is obtained five times more frequently than holds true in the population at large. All studies from the day of Little attest this fact, the incidence of premature birth in cases of cerebral palsy being reported as about 35 per cent, in contrast to 7 per cent in the population at large.[5] The role of prematurity in causing neuropsychiatric damage is also demonstrated by the longitudinal study of the sequelae of prematurity being carried out by Knobloch, Rider, Harper and Pasamanick.[6] In examinations performed at 40 weeks (adjusted for premature birth date) on 500 single-born premature infants, "overt neurological defects" were encountered in 2.1 per cent as against 0.6 in 496 carefully matched mature babies. No infants with a birth weight under 2001 gm. were considered to have a superior intellectual potential.

Another circumstance attesting the importance of obstetrical factors in the etiology of cerebral palsy is the poor condition of these infants at birth. This has been demonstrated in our own Clinic by an analysis of the obstetrical records of 96 infants who later had cerebral palsy.[5] All these infants were born at the Johns Hopkins Hospital, where our case histories provide a fairly complete and detailed picture of the whole course of pregnancy, labor and the neonatal period. The 96 cases of cerebral palsy were culled from various Maryland cerebral palsy clinics and hospitals. The hospital where the baby was born was then ascertained, either through the records of the clinics or hospitals visited or more often through the municipal office of vital statistics. As stated, only those infants who were born in our hospital were included in the series. The diagnosis of cerebral palsy had been made by specialists in this field as well as the type of neurological disorder present. In order to provide a basis for comparison, a control series of 11,195 infants who were born in our hospital between 1945 and 1949, and who survived, has been analyzed in respect to the same complications encountered in the cerebral palsy series. This period of time was chosen because most of the infants with cerebral palsy in the study were born during those years.

If there is any question about the importance of obstetrical factors in the etiology of cerebral palsy, it will be dispelled by a study of Table 14. It is routine in our hospital to record on the labor chart the condition of the baby at birth by encircling one of four printed words on the chart in the section dealing with the newborn. These words are "Good," "Fair," "Poor," "Dead." This designation on the chart states the clinical impression of the attending obstetrician or pediatrician of the condition of the baby as attested by its behavior during the first hour of life. This fact needs emphasis because in going back to the obstetrical records of these infants with cerebral palsy it should be made plain that we did not read into those histories any observations that had not been clearly

TABLE 14. *Condition at Birth of 96 Infants Who Later Had Cerebral Palsy Compared with Control Percentages*

CONDITION AT BIRTH	CEREBRAL PALSY SERIES				CONTROLS PER CENT
	Full Term	Premature	Total	Per Cent	
Good	34	14	48	50	87
Fair	4	5	9	9	11
Poor	24	15	39	41	2

recorded there at the time of birth. As shown in the last line of Table 14, the word "Poor" was encircled in 41 per cent of the cerebral palsy series, in contrast to 2 per cent in the control group. The reason for calling the condition of such a large number of infants "Poor" at birth was most frequently abnormalities of respiratory behavior, but in some cases it was flaccidity, cyanosis and the character of the cry. Most often a combination of these findings dictated placing the infant in this group.

The fact that many of the babies in the cerebral palsy series had already suffered severe damage before birth is revealed also by the breathing time of these infants, as shown in Table 15. Breathing times under two minutes showed about the same frequency in the cerebral palsy series and in the controls, but the extremely high frequency of prolonged breathing time in the cerebral palsy group is evidenced by the inordinately large proportion of these infants who showed a breathing time of more than two minutes. Most noteworthy perhaps is the fact that 13 per cent of the babies who had cerebral palsy did not breathe spontaneously for six minutes or more, whereas such an extremely long breathing time was observed in the controls only once in about 300 cases.

Further evidence that the cerebral palsy infants were gravely handicapped at the time of birth is shown by the prolonged duration of their hospital stay. The hospital stay of premature babies depends chiefly on

TABLE 15. *Breathing Time at Birth of 87 Infants Who Later Had Cerebral Palsy (Not Recorded in 9 Cases in Series)*

TIME	CEREBRAL PALSY SERIES				CONTROLS PER CENT
	Full Term	Premature	Total	Per Cent	
Immed.-5 sec.	30	22	52	60	72.0
6-29 sec.	7	2	9	10	14.7
30-59 sec.	5	1	6	7	8.0
60-119 sec.	2	0	2	2	3.5
120-179 sec.	2	0	2	2	0.6
180-239 sec.	1	0	1	1	0.3
240-299 sec.	1	1	2	2	0.2
300-359 sec.	1	1	2	2	0.2
359 sec. plus	9	2	11	13	0.3

the degree of prematurity and is not necessarily an index of their state of well-being over the neonatal period. On the other hand, the average stay of the mature babies in our hospital, as shown by the control series, was 5.3 days, and, with rare exceptions, any appreciable prolongation in the stay of mature babies is indicative of difficulty of one kind or another. The average stay of the 62 mature babies in the cerebral palsy series was 15.1 days. The pediatric records show that the conditions which most frequently necessitated such prolonged hospitalization were abnormal respiratory behavior, repeated attacks of cyanosis, feeding difficulties, prolonged, unexplained fever, and failure to gain in weight. Strangely enough, neurological signs and symptoms were encountered less frequently than the findings just mentioned, only five infants in the entire series of 96 showing actual convulsions. In sum, about half of the cerebral palsy infants showed clear-cut evidence of having sustained some form of intrauterine injury during either the antepartal or intrapartal period.

In addition to premature birth, the obstetrical complications most frequently associated with the later development of cerebral palsy, on the basis of our study mentioned above, are trauma, uterine bleeding after the twentieth week, intrauterine infection, and anesthesia accidents. Although in modern obstetrics the substitution of cesarean section for traumatic vaginal delivery has reduced the incidence of brain damage attributable to trauma, the evidence is clear that even today trauma at delivery is still responsible for many cases. Thus, in our group of 96 cases of cerebral palsy, the incidence of breech delivery, midforceps, shoulder dystocia and prolonged second stage was several times the frequency in the control series. Although our cerebral palsy group was small, these differences were significant at the 5 per cent level of probability. The importance of bleeding in the last half of pregnancy as a causative factor in cerebral palsy has already been emphasized by Lilienfeld and Parkhurst.[7] Bleeding and anesthesia accidents doubtless exert their effects on the fetal brain through the medium of hypoxia; and, in general, intrauterine hypoxia is thought to play a dominant role in the causation of cerebral palsy and other forms of neuropsychiatric impairment.

Congenital malformations of the brain undoubtedly play an important role in the causation of cerebral palsy and other related conditions, but precise data are lacking. Malformations in general have been reported by the National Office of Vital Statistics as responsible for 4.4 neonatal deaths per 1000 live births during the first three months of 1950. They accounted for 24 per cent of the deaths of infants weighing over 2500 gm. and 7 per cent of the deaths of infants weighing under 2500 gm.[10] Whether these malformations are the result of weak hormonal support, nutritional deficiencies, systemic disease of the mother

(such as early virus infections), or defective genes, is a moot question. But, in connection with the present discussion, it is important to note that about 40 per cent of all congenital malformations involve the central nervous system.[3] Moreover, in a study of neuropathology in 543 autopsies on mental defectives, Malamud classified 400 (74 per cent) of the brains examined as congenitally malformed.[9] This is a field in which intensive research is urgently needed.

Although Rh iso-immunization of the mother followed by kernicterus of the infant is an unquestionable cause of cerebral palsy, present opinion veers to the belief that this factor is responsible for only 1 or 2 per cent of all cases.* Exchange transfusion promises to lower this percentage to an even smaller figure. Thus Diamond has been able to reduce the incidence of kernicterus in erythroblastosis from 28.6 per cent in 1945 to 2 per cent and 3.3 per cent in 1949 and 1950, respectively.[4]

In view of the circumstances reviewed in the foregoing paragraphs, the consensus is that some two thirds of all cases of cerebral palsy are attributable to obstetrical factors. Although this is doubtless true, the exact role played by each of the many possible factors is virtually unknown. Even in the case of prematurity, although the association between cerebral palsy and premature birth is clearly established, the mechanism involved is obscure. Thus, in such cases, is it the immature state of the nervous system per se, possibly lack of myelination of certain important nerve tracts, which is responsible for the disease? Or is it rather the fetal hypoxia associated with the obstetrical complications, such as abruptio, which so often causes premature labor? Or is it the faulty pulmonary ventilation with resultant hypoxia which premature infants so frequently suffer during the early neonatal period? These and many other questions dealing with etiology must be answered before a fully intelligent approach to the prevention of cerebral palsy can be made. It is to answer such questions that the National Institute of Neurological Diseases and Blindness has sponsored its comprehensive Collaborative Study of Cerebral Palsy. It is to be hoped that this far-sighted program will elucidate in clear-cut terms the main causative factors of the disease. But this will require years; and, from a practical viewpoint, the pressing question is: What can obstetricians do today—with today's available knowledge—to prevent cerebral palsy?

The transcendent desideratum in the prevention of cerebral palsy is of course the prevention of premature birth. To make great inroads on this complication is avowedly difficult, but there are several measures which promise to yield some reduction in its frequency. The most important of these is more rest for the expectant mother in the last trimester of pregnancy. This fact has been emphasized in an important

* M. A. Perlstein: Personal communication.

paper by Stewart.[11] These authors classified 772 pregnant women of the same (lower) social class into the following three groups: (*a*) housewives not gainfully employed; (*b*) housewives gainfully employed, but not beyond the twenty-eighth week of pregnancy; and (*c*) housewives gainfully employed beyond the twenty-eighth week of pregnancy. The incidence of premature birth in these three groups was, respectively, 4.0 per cent, 8.5 per cent and 10.4 per cent. These figures speak for themselves and offer a reasonable explanation for the well known fact that the frequency of premature birth is related to socio-economic status. Since about 12 per cent of all premature infants stem from twin pregnancies, this injunction about the desirability of rest in the latter part of pregnancy is particularly pertinent to cases of multiple gestation. Moreover, since premature labor shows a pronounced tendency to repeat in subsequent pregnancies, a woman with a history of previous premature births should be especially warned about the importance of rest.

Still another category of women in whom premature birth is more common is the group characterized by bleeding either in the early months of pregnancy or from time to time throughout. Here, massive doses of long-acting progesterone (100 to 200 mg. twice a week) have proved of great efficacy in our own Clinic in prolonging certain pregnancies. The same therapy is also useful in patients whose membranes rupture when the baby is still premature. Finally, in certain cases of bleeding from placenta praevia expectant management of the case will sometimes make it possible to give the infant the advantage of continued intrauterine existence for as much as one to two months.

Another way by which obstetricians can conceivably diminish the frequency of cerebral palsy is through striving for spontaneous deliveries. In general, the condition of the baby at birth will approach the optimum *pari passu* with the degree with which this objective is obtained; and, as we have seen, there does appear to be a certain correlation between the condition of the baby at birth and the subsequent development of cerebral palsy. But is it actually true that the condition of the newborn is better after spontaneous delivery than after operative manipulations, even low forceps? If it be assumed that the degree of apnea neonatorum is a dependable index of the condition of the neonate (a reasonable assumption), Table 16 indicates that this question must be answered in the affirmative. Here it may be seen that the incidence of apnea neonatorum (defined as a breathing time of two minutes or more) was only 0.8 per cent in a series of deliveries in which there was neither operative procedure nor obstetric complication involved. But, even in the absence of obstetric complications, operative delivery per vaginam (mostly elective low forceps) more than doubled the incidences of apnea as so defined.

TABLE 16. *Incidence of Apnea Neonatorum According to Labor Complications and Operations, 7527 Vaginal Deliveries*
Johns Hopkins Hospital, 1952, 1953, 1954

	ALL DELIVERIES	
	Number	Per Cent Apneic
All deliveries	7527	1.6
No labor complications, no operation	4541	0.8
No labor complications, operations	1859	1.9
Labor complications, no operation	686	3.6
Labor complications, operations	441	6.1

A third way in which the frequency of cerebral palsy can probably be diminished is through the routine administration of oxygen to the mother during all, or at least the latter part, of the second stage of labor. Studies in our Clinic by Harry Prystowsky show beyond question that administration of oxygen to mothers in labor increases enormously the oxygen content of the intervillous space blood as well as that of the umbilical vein blood. This is effected presumably by augmenting the oxygen dissolved in the plasma. It is true that this measure may be unnecessary in most cases, but in certain cases of fetal hypoxia it may prove lifesaving, while in cases of sublethal hypoxia it is our most efficacious means of preventing brain injury.

The recommendations made above are simple, common sense measures directed at reducing both perinatal mortality and various sublethal types of brain injury of the fetus. If superimposed on sound antepartal care, including a well balanced diet and appropriate hygienic precautions, they should help greatly in achieving the high objectives at which they are directed.

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THE EARLY DIAGNOSIS OF CEREBRAL PALSY

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The term "infantile cerebral palsy" is usually reserved for those patients under the age of seven or eight years. By this age the patterns of growth should be established. It is estimated that in every 200 live births there is one case of brain damage, and that the distribution is even throughout the country.

The recognition of cerebral palsy in early infancy may be difficult in the first six to 12 months of life. The diagnosis in most cases with minimal brain damage is not often made during the early years of life. In one survey carried out in 1950 the diagnosis was missed in approximately 70 per cent of the patients between the ages of one and five. The many varied functional aberrations of the neuromuscular system resulting from brain damage depend on many factors. The site and magnitude of the lesion, and its nature, i.e., static or progressive, will determine the readiness of clinical recognition.

It is generally true in medicine that the history is often the most important factor in establishing a diagnosis, and this is especially true in pediatrics. History of the pregnancy, labor and delivery, and of the rate of growth and development, is essential not only for definite diagnosis, but also for prognosis.

ETIOLOGY

The etiology of cerebral palsy is classified in Table 17 under prenatal, natal and postnatal factors. Prenatal factors cause 30 per cent of all cases of cerebral palsy, natal factors cause 60 per cent, and postnatal factors cause 10 per cent. Although frequently there is no correlation between the clinical syndrome and the pathological findings, there is in certain specific etiologic factors a high correlation with certain neurologic sequelae. These are enumerated in Table 18.

TABLE 17. *Etiologic Classification of Cerebral Palsy*

I. PRENATAL—FROM TIME OF CONCEPTION TO ONSET OF LABOR
- A. Hereditary
  1. Static: genetically transmitted, often sex-linked symptoms present at birth or soon after, and does not progress; e.g., hereditary athetosis, familial tremors, familial spastic paraplegia
  2. Progressive: often not manifest at birth, though hereditary and progressive; e.g., Tay-Sachs disease, demyelinating diseases, tuberous sclerosis
- B. Acquired in utero
  1. Gonadal irradiation
  2. Prenatal infection; e.g., toxoplasmosis, rubella or other maternal infection
  3. Prenatal anoxia
     a. Maternal anoxia, anemia or hypotension
     b. Placental pathology; e.g., abruptio, infarcts, etc.
  4. Prenatal cerebral hemorrhage
     a. Toxemia of pregnancy
     b. Trauma
     c. Maternal bleeding diathesis
  5. Rh factor
  6. Metabolic disturbances; e.g., maternal diabetes

II. NATAL FACTORS—FROM ONSET OF LABOR TO VIABILITY OF THE FETUS
- A. Anoxia
  1. Mechanical respiratory obstruction
  2. Atelectasis
  3. Narcotism; e.g., after "twilight sleep"
  4. Placenta praevia or abruptio
  5. Maternal anoxia or hypotension; e.g., spinal anesthesia
  6. Breech deliveries, with delay of aftercoming head
- B. Cerebral hemorrhage and contusion
  1. Trauma
     a. Physiologic; e.g., disproportion, dystocia
     b. Obstetrical; e.g., forceps holding back head, labor inductions
  2. Sudden pressure changes; e.g., precipitate or cesarean delivery
  3. Constitutional factors
     a. Prematurity, congenital, syphilis
     b. Anemias of the newborn
     c. Hypoprothrombinemia

III. POSTNATAL FACTORS AFTER BIRTH OF VIABLE FETUS
- A. Traumatic, e.g.:
  1. Contusions of the brain
  2. Skull fractures
- B. Infections
  1. Acute; e.g., meningitis, encephalitis
  2. Chronic; e.g., syphilis, brain abscess, granulomas
- C. Vascular
  1. Hemorrhage
  2. Embolus
  3. Thrombosis
  4. Pressure changes; e.g., caisson disease
- D. Anoxia
  1. Carbon monoxide poisoning
  2. High altitude and low pressure anoxias
  3. Insulin reactions
- E. Neoplastic

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TABLE 18. *Correlation of Etiologic Factors in Cerebral Palsy with Neurologic Sequelae*

HISTORY	COMMON NEUROLOGIC SEQUELA
Prematurity	Spastic paraplegia
Breech delivery	Athetoid or spastic paraplegia
Toxemia of pregnancy	Spastic hemiplegia
Birth trauma	Spastic quadriplegia
Anoxia	Athetoid
Rh factor	Athetoid with deafness and paralysis of supraversion
Maternal rubella	Spastic with cataract, congenital heart
Precipitate delivery or cesarean section	Spastic quadriplegia or ataxia or rigidity

Clinical importance of etiology lies in high correlation between specific etiologic factors and clinical syndromes.

Only by the study of actual brain specimens will the pathogenesis of these conditions be well understood.

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The most common factors responsible for brain damage are anoxia and cerebral vascular injuries. Anoxia consists not only in the absence of oxygen, but also basically in the inadequacy of chemical oxidation for the utilization of glucose and other metabolites. The basal nuclei have a more active metabolism than the cortex, and as a result are more often affected by anoxia in the fetus. Because anoxia is blood-borne, the neurologic sequelae are usually symmetrical in extrapyramidal lesions.

The most common sequelae to cerebral vascular injuries are asymmetrical in distribution and pyramidal in nature. However, if there is extensive damage, the sequela is quadriplegic in distribution.

HISTORY

Family

The family history of convulsive seizures, neurological diseases, psychiatric diseases or mental retardation will be of aid in the diagnosis of heredo-degenerative disorders.

Prenatal

The prenatal history is extremely important, and special attention should be paid to the various stages of pregnancy.

1. First trimester: neurotropic viral infections result in severe brain damage and associated anomalies.

2. Second trimester: this is a period of iso-immunization; Rh incompatibility results in athetosis.

3. Third trimester: toxemia or anoxia may be the cause of ataxia or spasticity.

It is significant that approximately 30 per cent of cerebral palsied children and approximately 40 per cent of spastic paraplegics are premature.

Natal

History of the interval between the onset of labor to completion of delivery is extremely important, for 60 per cent of cerebral palsy cases are due to factors occurring in the natal period. The two most common factors are anoxia, and hemorrhage and trauma.

Anoxia may result from aspiration or from obstruction of the respiratory tract, cord around the neck, narcosis of the mother, placenta praevia and abruptio, sudden drop in blood pressure in the mother, hyperinsulinism in the diabetic mother, and breech deliveries. In breech deliveries the factors are injury plus anoxia, since delivery of the cord before delivery of the head means a potential period of anoxia.

Hemorrhage and trauma are most commonly caused by forceps deliveries, dystocia, prematurity, vitamin K deficiency and hypertensive encephalopathy.

Eclampsia in the mother results in a cerebral vascular accident in the fetus. Sudden change from intrauterine to extrauterine pressure, as in cesarean section or precipitate deliveries, may result in petechial hemorrhages. In dystocia over 90 per cent of the cases of brain damage are due merely to the hazards of being born.

In general, athetosis results from anoxia, while spasticity results from hemorrhage or trauma. In the natal period trauma and vascular injuries commonly produce spastic hemiplegia or quadriplegia. If the child is a spastic paraplegic, the damage most likely occurred in the prenatal period.

Postnatal

Postnatal factors account for approximately 10 per cent of cerebral palsy cases, the most frequent cases being spastic hemiplegias. The most common postnatal factors are accident, infection, aneurysm, hypertensive encephalopathy, toxic poisoning, tumors and brain abscess. A history of prematurity, anoxia or feeding difficulties in early postnatal life will suggest a diagnosis of cerebral palsy.

Development

Neuromuscular development is most prominent in the first through the third years, while emotional development is most prominent in the third through the sixth years. Hypotonia in the first year of life

may change into hypertonia as the central nervous system matures. With the increased tone, athetoid movements may become evident, or spasticity may appear. Table 19 lists the average range of ages for the functional development of the normal infant.

It is important in taking the history of the functional development to have the parents clearly understand your questions. If the mother is asked when her child spoke its first word, she will usually reply that "da-da" was the first word and "ma-ma" the second. This is incorrect, because these two sounds are universal and should not be regarded as words. Differential points should also be made as to the onset of true ambulation rather than walking with assistance. There are two things in the history that the mother has indelibly printed on her mind, and those are the exact birth weight of the child and the exact age at which the child first "walked."

TABLE 19. *Functional Development of the Normal Infant*

Controls head	6–12 weeks
Reaches	12–18 weeks
Sits without support	6–9 months
Crawls	6–8 months
Transfers objects from hand to hand	9–10 months
Speaks words	9–11 months
Stands alone	11–14 months
Walks alone	12–18 months
Speaks sentences	20–28 months

Seizures

Approximately 40 per cent of cerebral palsied patients have seizures, of varying degrees of both frequency and intensity. Seizures are more common in spastics (50 per cent) than in athetoids (18 per cent). As a general rule, the age at onset of seizures in the patient is more commonly in the period from birth to six months when these are due to brain damage. From six months up to six years the percentage of cases with seizures becomes progressively smaller in cases due to brain damage and larger in epileptics and in cases resulting from infections. Between the ages of six and 10 years 50 per cent of seizure cases are epileptic; over 10 years of age 70 per cent are epileptic. The most common types of clinical seizures in cerebral palsy are grand mal and focal. Petit mal and psychomotor types are less common.

EXAMINATION

General Physical Condition

Brain-damaged children are usually small but well proportioned. Cyanosis, pallor and poor head tonus may be signs of an anoxic infant. Persistent tonic neck reflex with clenched hands and poor head control

may be the first sign of a hypertonic infant. Frequently, however, hypotonia or atonia may be the earliest and presenting sign of a brain-damaged child. This will be discussed under Differential Diagnosis.

Abnormal skull contour does not necessarily mean that the infant has cerebral palsy. Head-chest relationship measurements, skull contour and status of the fontanel should be periodically checked.

Facial expressions are often an aid in differentiating between the mentally retarded and the cerebral palsied infant. It should be kept in mind, however, that hypotonia or atonia of central origin may be the reason for the lack of expression in a patient's face. Of course, in athetoid infants, there are excessive facial expressions which are unrelated to stimuli.

Persistent drooling after the age of one year is common in the cerebral palsied patient and especially in the athetoid. Many of the feeding problems of the athetoid may be due to the abnormal tongue movements.

Convulsions are present in 40 per cent of cerebral palsied children, the seizures being predominantly of the grand mal type. In comparison, convulsions occur in less than 1 per cent of the general population.

Neuromuscular Status

SPASTICITY. The presence of abnormal stretch reflex to rapid stimuli is characteristic. In addition, hyperactive deep tendon reflexes and pyramidal signs are usually present. The antigravity muscles are the most common site of the abnormal stretch reflex.

DYSKINESIA. The presence of an abnormal amount and type of involuntary motions is characteristic. The three main types of dyskinesia are athetosis, dystonia and tremor. Athetosis is characterized by an abnormal amount and type of involuntary movements, by normal reflexes and often by varying degrees of tension. In dystonia the tension is much greater, with a resulting slower involuntary type of motion. Tremors are uncontrollable, rhythmic, involuntary motions as contrasted to the sudden, jerky, rapid, involuntary movements found in chorea.

RIGIDITY. The presence of agonist-antagonist disturbance is characterized by resistance to slow passive motion. Resistance to passive motion may be the "lead-pipe" type (continuous) or the "cog-wheel" type (intermittent). Reflexes may be normal, or more often diminished, because of the presence of hypertonicity. The abnormal stretch reflex is absent, and the antagonist to the antigravity muscle is most commonly involved.

ATAXIA. Disturbance of kinesthetic and/or balance sense is present. Dyssynergia, "rebound phenomenon," astereognosis and depth perception involvement may also be present.

HYPOTONIA. Definite lack of tone is present, and, in some cases,

muscles may fail to respond at all to voluntary stimulation. Hypotonia may be the only sign in the early stage of infancy and should be differentiated between the central and spinal types. In the hypotonic infant the strychnine test may be used to differentiate the central from the spinal and the muscular types. Perlstein states that in the central hypotonias the administration of strychnine increases the tone of muscle and that this tone is not lost when the medication is withdrawn. Another differential point is the presence of the stretch reflex in the central hypotonic infant. When the loss of tone is severe, the term "atonia" is used.

In many cases there may be mixed motor symptoms with one type predominant; i.e., in the mixed spastic athetoid, athetosis is most commonly found in the upper extremities and spasticity in the lower extremities.

Reflexes

Tonic Neck Reflex. The tonic neck reflex is positive when there is extension of the limbs on the side of the body toward which the head is rotated and flexion of limbs on the opposite side. This reflex is normal in children until the sixteenth week of life; if it persists after this, brain damage is present.

Moro Reflex. The Moro reflex is a "startle" reflex also present in normal infants until the sixteenth week of life. The reflex is positive when the arms are thrown outward and then brought into an embracing motion when the infant is startled. If it is positive after the thirtieth week, brain damage is present.

Grasp Reflex. The grasp reflex, or "clenched-fist" reflex, is normal for the first three months of life. In brain-damaged infants this may persist for many months.

Stretch Reflex. The stretch reflex is elicited by rapid passive movement. In spasticity there is a lower threshold of the stretch reflex with an increased tendency of the muscle to contract. A sustained stretch reflex is termed "clonus."

Superficial reflexes are usually normal and are of little diagnostic significance for cerebral palsy.

Specific Tests

The following specific tests may or may not be necessary for diagnosis of an individual case.

Electroencephalogram. The greatest number of abnormal electroencephalograms are found in the four to six year age group, but they may be of diagnostic value after the age of three months.

PNEUMOENCEPHALOGRAM. This is done to rule out anomalies, tumors, internal hydrocephalus and subdural hematoma.

CEREBROSPINAL PUNCTURE. To detect hemorrhage, infection or block.

X-RAY. To detect developmental defects, or fractures, and to determine bone age.

LABORATORY. To determine Rh factors of the parents.

PSYCHOLOGICAL. To determine mental age and I.Q., and to differentiate between emotional and organic factors.

EYE GROUND EXAMINATION. To detect the presence of tumors, anomalies, infection, lens opacity or genetic disorders.

DIFFERENTIAL DIAGNOSIS

Many conditions must be considered in the differential diagnosis of cerebral palsy. Among the many possibilities other than those discussed below are food allergies, avitaminosis, malnutrition, endocrine disturbances, meningitis, encephalitis, poliomyelitis, cretinism, mongolism, familial degenerative diseases, Erb's palsy, congenital defects and isolated sensory defects.

In my opinion the following conditions are the most difficult to differentiate in the first years of life.

Mental Retardation

In the undifferential mentally retarded patient, developmental tests reveal equal retardation in motor, social, linguistic and adapted behavior. In these patients there is no evidence of spasticity, athetosis, ataxia or rigidity. In patients with mental retardation associated with cerebral palsy there is an unequal developmental rate in the four spheres, and presence of some neuromuscular aberration.

Amyotonia Congenita

The strychnine test may differentiate between the hypotonia of central or of spinal origin. If the hypotonia or atonia is of central origin, strychnine will increase the tone of the muscles. Clinically, the presence of the abnormal stretch reflex, though weak, is diagnostic.

Muscular Dystrophy

Family hisotry and age at onset are vital diagnostic hints. Muscle biopsy is of little value. Urinary creatine-creatinine studies are not diagnostic in early life.

SUMMARY

The diagnosis of cerebral palsy in infants is difficult. There may be no gross evidence of motor abnormality in the first 12 to 18 months. As the nervous system matures, there may be a change in the neurological pattern. Therefore, in the early months, the motor classification may be only tentative. But the diagnosis of cerebral palsy can be made early by taking a careful, thorough history and by the judicious use of certain specific tests and examinations. This diagnosis should be made early, not only so that a program of treatment can be begun early, but also to rule out, by the appropriate tests, lesions that are progressive and that may threaten the infant's life.

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THE DOCTOR'S RESPONSIBILITY IN THE PREVENTION OF POSTNATAL DISEASES OF THE BRAIN

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Since an intact brain is essential to successful competition in life, its preservation is of the utmost importance to the individual. Though we know of no means of improving cerebral endowment, we know of many factors contributing to its injury, and inasmuch as cerebral neurons do not multiply significantly postnatally, one of the important functions of doctors is to assume responsibility for their preservation. The purpose of this article is to direct medical attention to various situations in which proper diagnosis and treatment can preserve intellectual assets.

First, as to the magnitude of the problem, Yannet,[25] in a study of the causes for admission of the first 2000 mentally defective children to Southbury Training School in Connecticut, found postnatal causes to be responsible for 6 per cent of the cases. Malmud,[19] in a study of autopsy material, found that destructive lesions certainly postnatal accounted for about 2 per cent of the cases of mental retardation and that an additional 10 per cent had destructive cerebral lesions of unknown timing, either natal or postnatal. In a review of 1403 cerebral palsy cases Crothers and Paine found that postnatally occurring lesions were responsible for the defect in approximately 15 per cent of the cases.

Three peculiarities of life in the first few postnatal months or years are of importance in determining the susceptibility of infants and children to cerebral damage. The rapid differentiation and growth of the brain early in life is the first of these. During this time, recovery from cerebral disease not only requires restoration to the status quo ante, but also

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implies the continuation of orderly growth and development. Cerebral disease occurring early in life may readily prejudice the latter; for example, recovery from measles encephalitis at two years of age is more frequently followed by failure of normal intellectual development than is the case with a comparable illness at 10 years of age.[20]

Secondly, the young infant passes through a stage of relative defenselessness against infection after losing whatever antibodies were passively transferred to it by its mother during intrauterine life. Fothergill and Wright, for example, showed that antibodies against the influenza bacillus were usually inherited by babies in adequate amounts, but that these antibodies were lost in the first two months of life and gradually rebuilt to adult levels at about six or seven years of age. Influenzal meningitis rarely occurs in the first two months of life, is most common around three to six months and then becomes increasingly uncommon in childhood. Though the details of timing vary, similar phenomena obtain in relation to other infectious agents. During infancy, therefore, protection from overwhelming doses of infection by siblings assumes particular importance, as does protection by active and passive immunization.

Thirdly, the much richer venous connections from scalp to meningeal veins tend to increase the liability to venous hemorrhage in the meningeal spaces and of transport of infections or chemical agents from the scalp.

PURULENT MENINGITIS

Proper diagnosis, treatment and after-care of purulent meningitis is one of the most important situations in which medical acumen can contribute to the future intelligence and emotional well-being of the infant.

Meningeal infection rapidly and permanently impairs cerebral structure and function by direct inflammatory lesions of the brain (acute cerebritis) and by injury to both arteries and veins. Acute arteritis impairs the blood supply to the brain, and thrombosis of veins and dural sinuses results in venous infarction. In part, some of these cerebral lesions may be reversible, but, in the case of meningitis, their avoidance is of paramount importance and is a matter of time measured in hours or fractions thereof.

As pointed out by Alexander,[1] the means for the satisfactory cure of meningitis have been present and widely known since the middle 1940's, but blindness, deafness, mental retardation, cerebral palsy and epilepsy continue to present after meningitis in all too large numbers. These tragedies can be attributed to failure of early diagnosis, inadequate laboratory facilities for the identification of the infecting agent,

and improper selection of therapeutic agents and their use in inadequate doses. In addition, while the widespread policy of the use of moderate doses of antibiotics for the treatment of undiagnosed fevers results in fewer deaths from meningitis, a larger burden of surviving crippled children results.

Clinical Manifestations

The clinical signs of meningitis vary a great deal with age, and in premature and newborn infants are often vague. In such tiny babies cyanosis, vomiting and irregular respiration are usually present, fever and jaundice are frequent, and vague cerebral dysfunction such as jitteriness or somnolence may occur. Much valuable time is often lost in the consideration of such diagnoses as tracheo-esophageal fistula or congenital heart disease in these babies. Later in infancy fever, vomiting, jitteriness or somnolence, convulsions and, in the absence of severe dehydration, a bulging fontanel occur. The child with closed fontanel and more mature brain and skull shows the expected clinical picture of stiff neck, fever, headache, vomiting, drowsiness and convulsion. Kernig's and Brudzinski's signs are usually positive and *tache cérébral* is present.

Diagnosis

Examination of the cerebrospinal fluid obtained by lumbar puncture establishes the diagnosis, and should be obtained whenever the suspicion of meningitis arises. In the presence of choked discs (usually found in meningitis secondary to brain abscess or occasionally in tuberculous meningitis) puncture should be done cautiously and only 2 or 3 ml. of fluid removed. The important examinations are quantitation of the sugar, cell count, stained smear for organisms, and culture. If the puncture is done at home, a sterile sample of fluid should be sent with the patient to the hospital where treatment will be carried out. In purulent meningitis the sugar content is usually below 45 mg. per 100 ml.; the cell count is usually over 100 polynuclear cells per cubic milliliter, though in overwhelming infections in infants and little children it may rarely be normal; the smear shows many polynuclear cells and may show organisms (often seen better in methylene blue stains than by Gram's method); and the culture should be characteristic unless prior treatment with antimicrobial drugs prevents growth of organisms.

Treatment

Treatment should be vigorous and immediate; it is believed that the loss of a few hours before beginning treatment may prejudice results.

In our hands intravenous treatment has ensured adequate dosage of antibiotics, easy regulation of fluids and supplementary drugs. If, however, the establishment of an intravenous channel causes considerable delay, intramuscular treatment should be instituted at once. The drugs used should be specific so far as possible; probably, before identification of the responsible organism, a combination of aqueous crystalline penicillin, 200,000 units, chloramphenicol, 50 mg. per kilogram, and sulfadiazine, 100 mg. per kilogram, should be given intramuscularly or intravenously. *Hemophilus influenzae* meningitis should be treated with chloramphenicol, 100 mg. per kilogram per day intravenously; and sulfadiazine, 50 mg. per kilogram per day, is thought by some (Kock) to add to the effectiveness of treatment. Meningococcal meningitis responds promptly to sulfadiazine, 50 mg. per kilogram per day intravenously, or 200 mg. per kilogram per day by mouth if vomiting is not present. Pneumococcal meningitis should be treated with 1 to 4 million units of penicillin intravenously or intramuscularly every six hours plus sulfadiazine as recommended above. The coliform bacilli are resistant to treatment, and sensitivity studies should guide treatment. While these are being made, streptomycin, 50 mg. per kilogram per day, plus sulfadiazine and chloramphenicol as above should be used. Polymyxin B, 2.5 mg. per kilogram per day intramuscularly, with one dose of 2 mg. intrathecally can be used for four-day periods and sometimes may be successfully alternated with neomycin, 10 to 15 mg. per kilogram per day divided into four doses given intramuscularly every six hours.

Since both polymyxin and neomycin cause severe kidney damage after seven to 10 days, blood nonprotein nitrogen should be estimated and urine examined for concentration, albumin and sediment daily. Neither of these drugs should be used continuously for more than five to seven days, but can be alternated.

Treatment should be continued until the cerebrospinal fluid sugar has returned to normal levels and the cell count toward normal, usually three to five days for influenzal and meningococcal meningitis, and for at least a week after the fluid has become normal for the pneumococcal and coliform types, since relapses are common in these.

Complications

Complications of the disease are related in part to its severity. Subdural collections of fluid are found in young children and infants in various percentages by various observers in all types of purulent meningitis. Any infant or child presenting continuing evidence of neurologic disturbance such as headache, abnormal gait, mild hemiplegia or other focal neurologic signs or continued vomiting should be subjected to subdural puncture through the coronal suture if possible; if not, through

burr holes in the skull. If a collection of fluid is found and recurs in spite of several taps at intervals of a few days, membrane formation should be suspected and sought for by a neurosurgeon.

Localized abscesses of the brain occasionally occur and present themselves by a recurrence of fever and neurologic symptoms following cessation of therapy.

Prognosis

With more prompt and efficient treatment, results appear to be improving, but, since no good standards of evidence for brain damage exist in infancy, it is impossible to compare statistics. In a general way, however, it is thought that about 20 per cent of infants with pneumococcal infections will show serious damage, and that with less virulent infection and older children the results should be better. In neonatal cases effective recovery has been less frequent; less than 25 per cent in Watson's[24] series of 45 cases and, in our hospital,[12] about 20 per cent in a series of 27 with coliform infections. All neonates with streptococcal meningitis have died, no matter how treated here. Most of the neonates in whom permanent cerebral damage occurred have died within a three-year period.

TUBERCULOUS MENINGITIS

It seems probable that, as we become more proficient in the use of the means now at hand, this terrible disease can be nearly eliminated. Miliary and meningeal tuberculosis have not developed in a patient on adequate doses of isoniazid (doses in the neighborhood of 10 mg. per kilogram per day), though a few cases have appeared in children believed to be taking ineffective doses (approximately 4 mg. per kilogram per day). To whom, then, shall antituberculous drugs be given, since the prevention of tuberculous meningitis and adequate care of tuberculosis in general must go hand in hand?

Debré and Brissaud[7] in France and Frölich in Norway report the occurrence of tuberculous meningitis in 0.33 per cent and 0.39 per cent respectively of children of school age reacting to tuberculin and followed over 20 years. Miller[21] reported on follow-up studies on children under five years of age with primary tuberculosis during a two-year period following infection and found that 4.1 per cent had miliary and meningeal tuberculosis. In still younger children the prognosis is even worse; Le Meltier, as quoted by Debré and Brissaud, found mortality rates from tuberculosis in a six-year period among 134 infants infected between birth and three years to be 30 per cent for infants under six months, 14 per cent for those infected between six and 12 months, and 7

per cent for those infected between one and two years. It seems clear that little children infected with tuberculosis should be treated, and in addition Debré points to the increased risk of active tuberculosis in adolescent girls beginning at about 11 years and in boys at 13 years, and advises active treatment for them.

Robinson and Meyer[22] compared two groups of children with primary tuberculosis, one treated with antitubercular drugs and the other serving as controls, all followed up for about 30 months. Of 34 treated children, two had active tuberculous processes, and, of 35 control children, nine had active tuberculous processes, including two examples of meningitis. The two children on treatment in whom active disease developed were treated with streptomycin alone before the introduction of isoniazid.

Treatment

Treatment of primary tuberculosis should be preceded by chest x-rays and, in children under three or four, a lumbar puncture in addition, since early tuberculous meningitis in their age group may be nearly asymptomatic. These should be repeated two weeks after beginning treatment, lest treatment be abandoned too early.

Treatment for primary tuberculosis should consist of paraminosalicylic acid (PAS) at a rate of 300 mg. per kilogram per day in two divided doses by mouth. Isoniazid (I.N.H.) should be given in doses of 10 to 20 mg. per kilogram per day, by mouth in two divided doses, the larger dose for infants under two years, and in no event more than 400 mg. a day should be given to any patient. Babies under two should probably receive, in addition, streptomycin at a rate of 50 mg. per kilogram per day intramuscularly for the first month. Treatment should continue for about six to eight months, the younger the child the longer.

When the disease process has invaded the meninges, a long course of intensive treatment is required, and careful diagnosis is necessary to give one the courage to carry it out. In babies and young children vague complaints of vomiting and ill health often precede the usual meningeal signs of stiff neck and headache, and should, in infected children, lead to lumbar puncture. The characteristics of the cerebrospinal fluid are well known: lowered glucose content (below 35 mg. per 100 ml.), increase in cells, predominantly mononuclear, increased protein content, with fibrin accumulation to the point of web formation on standing in a test tube. The glucose content may, in the early stages of the disease, be relatively normal. Cultures on Dubos' and Lowenstein's medium and guinea pig inoculations of the cerebrospinal fluid, and gastric washings if possible, should always be made before treatment is begun. Lumbar puncture should be repeated two weeks after beginning treatment.

Treatment must be prompt, continuous and prolonged and should consist of:

Streptomycin, I.M. .... 30-40 mg./kg./day for 6 months
Isoniazid, P.O. ..... 10 mg./kg./day for 8 months
PAS, P.O. ..... 200-300 mg./kg./day for 8 months

Lorber[17] and others still advise the additional use of streptomycin intrathecally in doses of 25 to 50 mg. a day for 25 doses. Most observers feel that their results are as good without this painful addition to the regimen.

Foltz[10] and his co-workers have pointed out the frequency with which hydrocephalus occurs in tuberculous meningitis and advocate its surgical treatment early in the disease. No real controls are presented, however, and Lorber's paper contains serial ventriculograms suggesting the subsidence of such a lesion without treatment specifically aimed at it.

Since Shane and Riley[23] suggested the use of cortisone to reduce the inflammatory exudate and hydrocephalus thought to be secondary thereto in tuberculous meningitis, several series of cases so treated have been reported, including a series of 38 cases reported by Cocchi[4] with 97 per cent recovery. (He excluded those dying within 24 hours of admission.) This compares with a series of 69 treated by Lorber without cortisone with recovery rate of 85 per cent, including those brought in *in extremis*, or 91 per cent in those conscious on admission. Deaths from intercurrent purulent infection have occurred in several series in which cortisone was used. It may be that hydrocortisone intrathecally at a rate of 5 to 10 mg. a day may help in selected cases, especially when vision is impaired, but its use is not yet well established.

A few small series of cases of tuberculous meningitis treated by isoniazid alone at a rate of 10 mg. per kilogram per day orally for periods up to one year have been reported. Cures have certainly been obtained, and such treatment might be applicable in isolated situations, but is not yet generally accepted.

Recovery rates depend on early diagnosis and are poorer in infants than in older children because the vague symptomatology presented by the former tends to delay recognition of the disease. Effective recovery, should, however, be obtained in 80 to 90 per cent of patients.

Drugs used in the treatment of tuberculosis can produce serious toxic effects. Isoniazid produces peripheral neuritis when used over a considerable period. Adequate intake of vitamin B_6 (pyridoxine) will both prevent and relieve this condition. The accidental ingestion of large amounts of isoniazid by little children has produced severe and occasionally fatal convulsions with respiratory paralysis, beginning within minutes to an hour or so after ingestion Prevention is obviously accomplished by warning of the danger and proper storage of the drug in a locked

medicine cabinet. Treatment by prompt exchange transfusion and the use of a respirator appears to have been lifesaving in two instances.

Damage to the eighth cranial nerve with vestibular and occasionally auditory impairment is well known; its risk must at present be accepted in the treatment of tuberculous meningitis with streptomycin.

VIRAL MENINGITIS

Viral meningitis may occur at any age, and is usually characterized by headache, stiff neck and back, fever, prostration and vomiting. The cerebrospinal fluid usually contains mononuclear cells, the sugar level is usually 45 mg. per 100 ml. or above, and cultures and smear are negative for organisms. Mumps is the commonest cause of such meningitis, and the disease may present in the nervous system before parotid or other visceral involvement. Vaccine against mumps is at present under development, and may make mumps as unusual as diphtheria is now. Poliomyelitis is usually accompanied by a meningitis of this type, and, though the present vaccine is probably not completely effective in prevention, its administration is recommended until attempts to develop better vaccines are succesful. Poliomyelitis is recognizable at present by viral culture of the stool, and by the development of anterior horn cell involvement with paralysis.

Other types of viral meningitis, such as that caused by certain members of the Coxsackie group, can occasionally be identified etiologically by viral studies, but, since no specific treatment is available, such studies are principally of academic interest at present. Occasionally, in the course of or preceding infectious mononucleosis, a meningoradiculitis is found, and, though the cerebrospinal fluid usually shows a high protein content and relatively few cells, it sometimes contains several hundred mononuclear cells.

Differentiation from diseases requiring specific forms of treatment is of primary importance. These are principally tuberculous meningitis, leptospiral infections and pyogenic infections impinging on the meninges and bringing about cellular reaction in the cerebrospinal fluid. Early in its course tuberculous meningitis may exhibit a fairly normal cerebrospinal fluid sugar, but repetition of the examination a day or two later, if there is any clinical doubt, will differentiate. Infected dermoid cysts and epidural abscesses from other causes may also be confusing, but generally a careful physical examination will reveal local foci of infection or dimples over the spine or occiput indicating the presence of a sinus tract leading from skin to meninges. Such midline sinus tracts, if found on routine physical examination, should be referred for excision to a neurosurgeon because of the frequency with which they lead to meningitis.

ENCEPHALITIS

Only those forms of encephalitis for which some preventive measure is applicable will be mentioned.

Rabies

Among the so-called primary encephalitides only rabies can be prevented. Rabies[11] can be contracted rarely by contact of the apparently unbroken skin of children with saliva from a rabid animal, more frequently from bites through clothing and, in a still higher percentage of cases, by bites on the exposed skin of the hands, and, with the highest incidence of all, by bites on the head and neck. Bites in the latter regions have such a short incubation period that immunization by various forms of vaccine may not produce immunity sufficiently rapidly to forestall this universally fatal disease. Apparently most mammals are susceptible to the disease, and the saliva of infected animals is infectious, as is the milk of lactating infected animals. Bats appear to be capable of developing the carrier state, but in other animals infection always leads to death. For bites in the trunk or extremities or for persons associating with rabid animals or patients, the ordinary treatment with standard vaccines is effective. In countries such as Iran, where rabies is common, the 21-dose vaccine appears superior to the 14-dose treatment commonly favored in this country. For bites about the head and neck the use of immune rabbit serum in two, three or four doses on alternate days concurrently with vaccine treatment appears to give almost complete control of the disease. In a patient whose skull was crushed by a rabid wolf bite, six doses of serum and vaccine treatment resulted in prevention, an unprecedented success.

In addition to the vaccine, treatment with antibiotics is, of course, an important adjunct, as are antitetanic treatment and immediate local care of the wound by thorough irrigation with saline solution.

Vaccine carries a small risk of a secondary polyneuritis or myelitis, which is thought to be due to sensitization to the heterologous rabbit spinal cord which it contains. It should, therefore, be used with caution, and proof of exposure to rabies is the best indication.

When the question of whether a specific animal is rabid arises, it should not be killed, but should be confined for observation for two weeks; survival for this period eliminates the possibility of rabies, except possibly in bats. If the animal shows symptoms suggestive of rabies in the meantime, it should be killed and the brain examined microscopically for Negri bodies and biologically by injection into mice. Destruction of the brain by a bullet in the head successfully prevents diagnosis

Other Primary Encephalitides

Since at present there is no means of controlling or ameliorating other primary forms of encephalitis such as the equine, St. Louis or von Economo's types, no attempt to describe them is made here.

Secondary Encephalitides

Secondary encephalitides occur as an aftermath of various diseases, and occasionally follow the use of vaccine, both living and dead. The viral diseases of childhood are particularly potent in this regard. The morbidity of *encephalitis following measles* can be definitely reduced by using a modifying dose of gamma globulin in exposed persons, and a preventive dose is recommended in infants exposed during the second half of the first year of life when their maternally induced passive immunity has subsided. The main objection to the use of modifying doses of globulin is that it appears to diminish somewhat the chance of acquiring measles at any given exposure, thus tending to delay the disease to adult life, when its effects may be more severe.

The *encephalitis complicating whooping cough* seems definitely related to age and is mainly a disease of the first two years of life. Effective immunity can be conferred early in life by the use of pertussis vaccine combined with diphtheria and tetanus alum-precipitated toxoid, and should be begun as early as the third month of life, since there is no inherited immunity to the disease. Children of families with new babies should have been previously immunized so that they will not impart the disease to their newborn sibling. Passive immunization in babies exposed before the establishment of active immunity is possible with rabbit antiserum or hyperimmune human serum or hyperimmune pertussis gamma globulin, but it is frequently difficult to trace exposure to pertussis.

The *encephalopathy accompanying roseola* appears to be rather different from other diffuse inflammatory cerebral diseases in that it tends to leave behind it focal permanent residua such as hemiplegias combined with more or less severe diffuse cerebral damage. Though there is little pathological evidence, the course suggests vascular occlusion more than diffuse inflammation; and it seems likely that proper attention to hydration, such as the maintenance of an adequate urine output, and to fever by the use of salicylates and tepid sponges, might reduce the incidence of these disastrous sequelae. In roseola vomiting is seldom troublesome, and oral medication and fluids usually suffice. A urine specific gravity between 1.010 and 1.020 is an adequate measure of hydration in the absence of renal disease.

Encephalitis following vaccines has been reported after almost all

types of vaccines and serums. Of particular interest to pediatricians are those following smallpox vaccination and pertussis inoculation. The former have been particularly common in certain regions, but the New York experience of some 40 cases in some 6 million vaccinations is representative. The only apparent method of diminishing the chance of this complication is to vaccinate infants under one year of age, since the Dutch statistics indicate that the disease is about 30 times as frequent in children vaccinated for the first time between five and 10 years as it is in early infancy.[5]

Encephalitis following pertussis vaccination was reported rather frequently during the use of the original watery suspensions of killed *H. pertussis*.[3] Since the use of the vaccine combined with alum-precipitated toxoids of diphtheria and tetanus, such accidents appear to have become rare, and certainly far less common than the devastating results of pertussis itself in infants.

In little infants especially, an acute *encephalitis* marked by cerebral swelling may *accompany* overwhelming *infections*, especially with the streptococcus and pneumococcus. This disease is often so brief that the babies are found dead in bed. Short of this outcome, however, some babies found *in extremis* respond by astonishing recovery after the use of intravenous sulfonimides or penicillin. If possible, a blood culture should be obtained first, but such an illness is a most critical emergency, requiring vigorous treatment with an immediate dose of sulfadiazine, 50 mg. per kilogram intravenously or, if this is impossible, intramuscularly, or aqueous penicillin, 200,000 units in the same manner.

CONGENITAL ANOMALIES

A few congenital anomalies may have a progressively damaging effect on the brain. Among these, hypothyroidism, cranial synostosis and hydrocephalus are reasonably frequent, and their prompt detection followed by adequate treatment may well spell the difference between an effective life or a crippled one for the affected infant. Though galactosemia is rare, its recognition is likewise of the utmost importance from a cerebral point of view, as may possibly be the case for phenylketonuria.

Hypothyroidism*

Hypothyroidism, or sporadic cretinism, is the result of congenital hypoplasia or absence of the thyroid gland. There is some dispute as to whether maternal thyroid hormone crosses the placental barrier. Be that as it may, some cretins show delay in the development of certain epiph-

* See also pages 849 and 863.

yses, such as the distal epiphysis of the femur, normally present at birth. In such instances the results of treatment will probably be poor, since the thyroid defect has probably been present prenatally.

The early *diagnosis* of cretinism depends on a high index of suspicion on the part of the doctor for such symptoms and signs as constipation, thick skin, bizarre facies, large tongue, yellow skin, poor appetite, slow pulse and failure to grow. The diagnosis is crystallized by measurement of the serum protein-bound iodine, which in infants should normally be between 4.5 and 7.5 micrograms per 100 ml., and this measurement is also the best widely available method for controlling treatment. (Cooke[6] and others have shown that the butanol-extractable iodine measurement, when available, is slightly more accurate.) Delay in the appearance of epiphyses as demonstrated by x-ray film is far too nonspecific to be diagnostic, but if, for any reason, serum iodine levels cannot be followed, it is the second best method of controlling thyroid medication. Texture of skin, hair, tongue and the like are most unreliable guides to treatment, since they are affected favorably by doses of thyroid insufficient to stimulate normal osseous and cerebral growth.

Cooke has pointed out that, as judged by serum iodine levels, most infants with cretinism are inadequately treated. It is also a fact that thyroid preparations vary widely in physiological effectiveness from manufacturer to manufacturer, from lot to lot, and with time of storage. Pickering[9] and his associates have shown that l-thyroxin has the advantages of standard activity and more rapid therapeutic effect, an advantage probably of considerable importance when infantile cerebral development is concerned. They recommend beginning *treatment* in infancy with 0.1 mg. of l-thyroxin daily, increasing by 0.05 mg. daily in a week or 10 days, controlling dosage by serum protein-bound iodine levels, and aiming at levels of 7 to 10 micrograms per 100 ml. (These determinations can be made on 5-ml. sterile serum mailed to Bioscience Laboratory, 2231 Carmelina Avenue, Los Angeles, and Boston Medical Laboratory, 19 Bay State Road, Boston, Massachusetts.) Control of dosage by bone age, keeping it ahead of the normal age, is as reliable, but, since changes take place more slowly, proper adjustment of dosage is not as quickly achieved.

As a therapeutic agent l-thyroxin does not cause thyrotoxic symptoms until blood protein-bound iodine levels of over 12 micrograms per 100 ml. are attained; whereas, because of its local effect on the gastrointestinal tract and heart, desiccated thyroid may. Since treatment must be continued for life, proper diagnostic evidence should always be in the hands of the parents, and later the patient, in the form of a written blood iodine level, photograph of the baby and x-ray study of the wrists before and after treatment.

Galactosemia

Galactosemia[13] is an inborn error of metabolism in which a coenzyme essential to the conversion of galactose 1-phosphate to glucose-1-phosphate is missing and galactose piles up in the blood and diffuses into the tissues in abnormal amounts. Blood, and presumably tissue glucose levels, are secondarily depressed to pathological levels.

Galactosemia manifests itself almost with the first milk meal by loss of appetite, failure to thrive, large liver and spleen, jaundice, failure of mental development, and cataracts. Since there is no renal threshold for galactose, it appears in the urine whenever present in the blood stream, and the tip-off to galactosemia is the finding of a reducing substance in the urine in the presence of a relatively normal blood sugar. It can then be identified by the characteristic osazone formed with phenylhydrazine and by the fact that it is not fermented by ordinary yeast. The diagnosis can, according to Hartman, be clinched by giving a test dose of 1.75 gm. of galactose per kilogram and following the blood levels at hourly intervals. In galactosemia they reach 250 or more mg. per 100 ml., as opposed to 60 or 80 per cent in normals. The condition is also accompanied by aminoaciduria and impaired tests of hepatic function.

Treatment by complete withdrawal of milk and milk products from the diet is effective in early infancy, rapidly reversing the deleterious effects of the disease; but later in life mental retardation is not ameliorated. The milk-free diet must be continued for months or years and can be relaxed only when a more normal metabolism for galactose is indicated by failure of recurrence of aminoaciduria and lowered liver function tests following ingestion of galactose for a week or two.

Idiopathic Hypoglycemia

Idiopathic hypoglycemia[18] is probably a genetically determined disease of infancy. A history of the disease in siblings is not infrequent, and males are affected about twice as frequently as females. The onset of symptoms is usually within the first two years, occasionally as late as five years. The manifestations are episodes of limpness, "wilting," nervousness, irritability, dizziness, pallor, cold sweats, flushing, rolling up of eyes, unawareness, coma and sometimes convulsions. These are the same symptoms seen in diabetics overdosed with insulin. There are no physical stigmata, save that, in time, mental retardation and deterioration occur in untreated cases. Laboratory evidence consists in a fasting blood sugar below 40 mg. per 100 ml. and often below 30 mg. The electroencephalogram often shows high voltage slowing at a rate of

2 or 3 per second during attacks, and at times fairly well formed spikes may be seen between the slow waves.

Because of the episodic nature of the disease and the abnormal electroencephalogram, a diagnosis of epilepsy is usually made, and treatment on this basis given for so long that irreversible cerebral damage occurs. The disease must also, according to McQuarrie, be differentiated from adrenocortical insufficiency (Addison's disease), pituitary insufficiency (dwarfism), pancreatic tumor (rare if ever in childhood), hepatic disease, von Gierke's glycogen storage disease, galactosemia and severe hypothyroidism.

In most instances *treatment* with adrenocorticotropin, 4 mg. per kilogram per day divided into four doses and continued for three or four days, brings the condition under control, after which the dose may be reduced to about 1 mg. per kilogram per day given in two doses in the form of Acthar Gel.

The dose must be regulated by fasting blood sugar determination, and in most instances can be gradually reduced to zero over a period of eight months to a year. One instance, with onset in the first few days of life, which could not be ascribed to any other cause and could not be controlled by ACTH alone, required removal of seven eighths of the pancreas before a normal blood sugar could be maintained. (No tumor was found in serial section of the removed pancreas.)

Phenylketonuria

Phenylketonuria[14] is a metabolic defect in the conversion of phenylalanine to tyrosine, the result of failure of normal enzyme formation. It is inherited as a mendelian recessive, and can be recognized a month or so after birth by urine examination. It produces mental retardation, usually of a severe degree, epilepsy and often eczema and failure of normal pigment formation. The characteristic laboratory finding is a green color in fresh urine upon the addition of a few drops of glacial acetic acid and enough ferric chloride solution to precipitate the phosphates and leave an excess of ferric ions. Recent publications suggest that a diet low in phenylalanine and begun in the first two or three years of life may be effective in ameliorating the mental retardation. In patients past three years little effect on mental development seems to occur.

Craniosynostosis

Craniosynostosis[15] is a hereditary defect occurring sometimes in ancestors or siblings, or in both. The disease is characterized by fusion of one, some or all of the cranial sutures at or soon after birth. Various

deformities of the skull occur, and if the entire length of either the coronal or sagittal suture is involved, confinement of the growing brain occurs and results in mental retardation. It is frequently accompanied by other congenital anomalies, especially syndactylism.

The main *symptoms* are cranial deformity, prominence of eyes and occasionally papilledema, mental retardation and convulsions. The *diagnosis* is evident on x-ray examination of the skull, and, if made in the first three or four months of life, prevention of mental retardation is possible by surgical procedures. The intellectual results in infants suffering from synostosis of the coronal suture appear to be better than in those suffering from synostosis of the sagittal suture, though the cosmetic results unfortunately are the reverse.

Infantile Hydrocephalus

Infantile hydrocephalus[15] is the result of a variety of pathological lesions, anomalies, neoplasms and inflammations. In common they interfere with the cerebrospinal fluid circulation or absorption, and in common they cause dilatation of all or various portions of the cerebral ventricular system by increasing intraventricular pressure.

Too rapid enlargement of the head, best detected by comparing the hat-band measurement with standard growth charts, is the diagnostic measure most likely to disclose the condition early. A bulging fontanel is always present with the baby in the upright position, if the disease is active. In the more severe cases downward displacement of the eyeballs is obvious; irritability, vomiting, somnolence and motor disturbances appear. If the ventricles are considerably dilated, spasticity of the lower extremities is usually present.

An abnormally rapid enlargement of the head may occur when brain mass is increased by such diseases as Schilder's disease, Hurler's syndrome and lead poisoning, but in these ventricular size and pressure are not increased together, and x-rays of the skull seldom show separation of the sutures comparable to that seen in hydrocephalus, though ventriculography may be required to differentiate.

Several effective operations have been devised for dealing with this condition, each applicable in special circumstances as a result of careful neurosurgical investigation. Among these is the arachnoidureteral shunt, which is mentioned here since it results in obligatory loss of electrolytes, principally sodium and chloride, in the urine. After this operation the addition of 2 to 4 gm. of salt per day to the diet, or parenterally if the child is sick, is necessary to maintain electrolyte balance in the body fluids; omission of this precaution in infancy has led to unnecessary fatalities.

The important point for the medical man is to recognize the condi-

tion early and to refer the infant for neurosurgical care in the early months of life.

CEREBRAL INJURY SECONDARY TO DISTURBANCES IN WATER AND ELECTROLYTE BALANCE

Cerebral injury[8] may result in infancy from hemoconcentration and cerebral thromboses, or by an increase in sodium concentration in the body fluids. Since dehydration and its deleterious effects are well known, it and cerebral thrombosis secondary to these are seldom seen at present.

Hypernatremia is less well understood and presents a threat to future cerebral competence in infants. It is seen almost entirely in infants during the first half year. In the first two or three months of life it may accompany any infection, but in older infants it usually is induced by diarrhea. In either event cessation of fluid intake precedes it. Its symptoms are impairment of consciousness, excessive irritability when aroused, muscular twitchings, exaggerated tendon reflexes, and even convulsions. The diagnosis is suspected on history and clinical signs, and confirmed by the finding of a serum sodium level of 150 or more mEq. per liter. In addition, elevation of the cerebrospinal fluid total protein is found in over 90 per cent of cases.

Deaths results in about 10 per cent of cases, and cerebral damage of a permanent nature in a smaller proportion. Cerebral damage is probably the result of loss of intracellular fluid, accompanied by a loss of potassium, and, in addition, the serum calcium level is frequently depressed. Prevention by the administration of watery fluids instead of milk by mouth in the absence of vomiting, or in the presence of the latter parenteral administration of fluids, is simpler than treatment. Normal saline contains 0.9 gm. of sodium chloride per 100 cc., or about 150 mEq. per liter of sodium; for infants below one month, about 50 cc. per day meets their sodium needs, 100 cc. for infants up to six months, and 150 to 250 cc. for older infants. With this, 5 per cent glucose in water should be given to cover fluid needs, at a rate of about 150 to 200 cc. per kilogram. (Ten per cent glucose generally produces diuresis in infants and defeats its purpose.)

In the presence of hypernatremia (easily determined by flame photometry) sodium will still be required in the foregoing amounts or somewhat less, but, because of cellular water loss, potassium-containing fluids are required. These should be administered only after hydration has produced adequate blood flow and urine output. If they can be given as clear broth by mouth, chemical regulation is usually automatic. If not, a single dose of 50 to 80 cc. per kilogram of Darrow's solution may be given on one day followed by 20 to 40 cc. per kilogram per day

as long as diarrhea lasts. Calcium deficit in the serum can be made up by adding calcium gluconate to the intravenous fluids.

The important point to be made is that in very young infants water is usually lost in diarrheic stools faster than salt, and the indiscriminate use of normal saline solution is dangerous, and should be used only to maintain extracellular chemical balance, while glucose solution supplies the water required for active metabolic and excretory functions.

TRAUMA

Cerebral trauma[15] may be open or closed. Open trauma implies the establishment of direct communication between the outer world and the subarachnoid space. It may show itself directly or by leakage of cerebrospinal fluid from ears, nose or into the pharynx. Such trauma is at once a sign for generous antibiotic treatment and care as soon as possible by a neurosurgeon.

Closed trauma is by far the commonest type, and its proper evaluation and care depend more on serial observation of specific neurological signs and symptoms than on x-ray examination and routine lumbar puncture. Every child rendered unconscious by a blow on the head should be observed; if the stunning was momentary, this can be done at home. There the child should be observed at three hourly intervals at first to determine equality of pupils, ability to move extremities and level of consciousness even if this means waking him at night. The development of increasing headache, vomiting, inability to move an extremity, or inequality of pupils requires immediate medical evaluation, preferably in a hospital. If none of these signs eventuate, the child may be returned to activity in a day or two and the parents should be told with certainty that sequelae will not occur.

In more severe head injuries with unconsciousness of any duration, observation in a hospital by competent surgeons or neurosurgeons is essential. In transporting such an unconscious patient the back should be kept hyperextended and signs of other injuries should be sought lest a simple fracture be converted to a compound fracture or hemorrhage from a ruptured viscus be overlooked. The child should be placed so that secretions run from his mouth, or an airway should be installed by direct laryngoscopy, or the pharynx should be kept clear by mechanical suction. The development of signs of severe shock suggests hemorrhage elsewhere than in the head. The usual mild shock of concussion responds to warmth, rest and relief of pain.

Of great importance in such cases is frequent recording of the so-called vital signs; temperature, rate and regularity of pulse, blood pressure, and respiratory rate and rhythm at 15 to 30 minute intervals. Such a record should be begun before transportation.

LEAD POISONING

Lead poisoning may damage the cerebral structures by acute cerebral swelling with obstruction to blood flow, or more subtly by interference with normal processes of cerebral maturation.

In most cases chewing of lead-containing paint off furniture, window sills or mouldings, or eating flakes of such paint which have fallen to the floor or the ground is the source. Almost any chemical laboratory can determine whether such paint contains lead, and its approximate concentration. Lead content of over 5 per cent is certainly injurious, and, in the case of flaked paint, concentration of lead as low as 1 or 2 per cent may be.

If a source of lead can be identified, lead poisoning may be diagnosed with certainty if symptoms or signs from two of the following groups are present: (1) anemia, often with stippled red cells; (2) vomiting, cramps and constipation; (3) coproporphyrinuria; (4) glycosuria with normal blood sugar; (5) x-ray evidence of increased density at the lines of provisional calcification of the metaphases of the long bones; (6) encephalopathy, peripheral motor weakness or increased cerebrospinal fluid total protein.

If no source of lead is recognizable, the presence of symptoms or signs from three of these groups makes a diagnosis of lead poisoning mandatory. Any one of these symptoms and signs can be produced by agents other than lead.

The excretion of more than 80 micrograms of lead per 24 hours in a sample of urine collected in pyrex glass lead-free containers is clear evidence of the disease, but may not be present in severe encephalopathy because of deficient renal blood flow. A blood lead level above 4 micrograms per 100 ml. is also indicative of lead poisoning in most instances.

The laboratory diagnosis is not nearly as reliable as a diagnosis based on the chemical recognition of a source and clinical examination of the patient.

Treatment of the disease with edathemil (Versene) intravenously or subcutaneously is the best at hand. It should be given in doses of 1 gm. per 15 kilograms of body weight divided into two doses and given over a period of one or two hours each time. This should be continued for three to five days, and a second three-day course should be given after a five-day rest period, since the continuous use of edathemil for more than seven or eight days may produce irreversible renal damage. Versene by mouth is far less effective, and in the presence of lead in the gastrointestinal tract may promote the absorption of lead and cause a fulminating encephalopathy. Hydration of the usual sort tends in lead encephalopathy to increase the cerebral edema and should be avoided until brain swelling is subsiding, but, since edathemil induces excretion

of lead through the kidney, enough fluid to produce a urine flow of 200 to 400 cc. per 24 hours is needed.

Under edathemil therapy the cerebral symptoms subside, but only after one or two days, and for this reason, in patients with high intracranial pressure as shown by slow pulse and respiration and vascular hypertension, widespread cerebral decompression as practiced by Ingraham and Matson may be lifesaving.

After-care is as important as diagnosis and medicinal treatment. Virtually all patients will return to their fondness for paint chewing, and removal of all lead paint or covering it with metal counter mouldings is essential to the continued health and mental development of these children. Flaked paint should be scraped off and swept up, or buried under several inches of dirt.

CONGENITAL HEART DISEASE

Congenital heart disease accompanied by a right-to-left shunt, usually with cyanosis and polycythemia, is a threat to cerebral integrity. Thrombosis of cerebral arteries frequently occurs, especially in hot weather, as a result of hemoconcentration, and can probably be minimized by maintenance of a high fluid intake, particularly when sweating occurs in relation to hot weather or exercise. Children with such malformations are occasionally injured by dehydration prescribed for procedures such as intravenous pyelography.

Infected emboli may pass directly from the lungs to the brain, in the presence of a right-left shunt, resulting in cerebral or cerebellar abscess.[15] Headache, vomiting, fever and focal neurological and electroencephalographic signs are usually present. The cerebrospinal fluid may remain surprisingly normal in the early stages, or show simply elevated pressure.

Since these abscesses are usually unilocular, they yield readily to surgery, and early suspicion of their presence simplifies the neurosurgeon's task and improves the patient's prospects of recovery.

SUMMARY

An attempt has been made in the article to point out situations in which recent advances in medicine have in some way modified the usual approach of doctors to various problems. No attempt has been made to treat such subjects as intracranial tumors (the neurosurgical therapy of which has vastly improved in the past decade), arteriovenous malformations, congenital intracranial aneurysm, and the like.

It is also important to keep in mind that the developing child's brain is readily injured by such stresses as anoxia (in anesthesia, smoke inhalation, drowning, enclosure in tight boxes), hyperthemia (from disease,

overclothing, injections, sun stroke), ischemia (hemorrhage, shock), and that these may be found in a wide variety of situations which the doctor should be prepared to combat on the basis of indications gathered on the spot.

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PSYCHOLOGICAL ASPECTS OF THE MANAGEMENT OF CHILDREN WITH DEFECTS OR DAMAGE OF THE CENTRAL NERVOUS SYSTEM

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Disturbances in psychologic development are an integral part of the total problem presented by children with handicaps due to defect or damage of the central nervous system. The nature of the psychologic disturbances which develop depends upon the severity of the defect, the type and multiplicity of the functions predominantly involved, the age at onset, the integrative capacity of the child and the parents to deal with the problem, the physician's approach to management, and the availability of community resources.

Psychologic disturbances may be sufficiently severe in many instances to interfere with maximal compensation for the basic neurologic involvement, to result in neurotic or psychotic behavior, or to lead to psychosomatic disease. Ultimately psychologic difficulties are often the determining factor between social adequacy and inadequacy, which is the final criterion of the success of management of the affected person. Unfortunately, those children who have the most severe central nervous system involvement in early infancy are apt to have the most severe and lasting psychologic handicaps.

DISTURBANCES OF NEUROLOGIC FUNCTION IN CHILDHOOD

Table 20 lists some of the disturbances of function which are indicative of organic involvement of the central nervous system in childhood. A spectrum of severity exists for each of the disorders which may occur.

In addition, severity may be increased by multiplicity of involvement, because neurologic disease often is not localized, and disturbances in function tend to be multiple rather than single.

TABLE 20. *Disturbances of Function Indicative of Defect or Damage of the Central Nervous System in Childhood*

"MAJOR"	"MINOR"
Mental subnormality	Visual defects
Convulsions, recurrent	Auditory defects
Motor disorders:	Language defects (speech, aphasia, reading disability, etc.)
Spasticity	Perceptive defects
Athetosis	Conceptual defects
Hypotonicity	Irritability
Flaccidity	Impulsiveness
"Organic" behavior disorder (Laufer et al.[11])	Disturbances in cerebral dominance
	Sphincter disturbances
	Dysautonomia

EFFECT OF NEUROLOGIC DYSFUNCTION ON PSYCHOLOGIC DEVELOPMENT

Basically, the severity of neurologic disturbance in relation to the production of psychologic problems depends upon a potentiality for disrupting interpersonal relationships, and the age at onset tends to determine the seriousness of the psychologic results.

If the disturbance in neurologic function affects the neurologic pathways on which reciprocal maternal-infant relationships depend in the early weeks and months of personality formation, psychologic problems are likely to be severe. These problems are the primary result of the interference of the neurologic disturbance with the normal processes of personality development and may occur in the absence of conscious awareness by the mother. Frequently the sensory and perceptive pathways by which a mother normally communicates comfort to her infant are the ones affected. A congenital hearing defect is an example of such a sensory pathway which might be impaired in early infancy without the mother's knowledge, but other sensory modalities utilized in maternal-infant communication also may be affected. These include the following: tactile, kinesthetic, vibratory, temperature, visual, olfactory, pain and position sensations. Psychologic disturbance thus may be an inevitable consequence of the neurologic disturbance and so intimately a part of the total symptomatology that it cannot be recognized later as separate from the underlying neurologic disease.

It has been recognized since the ablation studies of Kennard[7, 8, 9] that functional compensation for a neurologic lesion tends to be most nearly complete if the lesion is produced early in life. The converse tends to be true of psychologic disturbances; the earlier in life these occur, the less

satisfactory the final compensation is apt to be, as the literature concerning maternal deprivation extensively illustrates.[3, 5, 13] Thus an infant who experiences neurologic and resultant psychologic disturbances from the time of birth may compensate partially in time for the neurologic lesion, only to remain permanently handicapped by the psychologic difficulties.

RELATIONSHIP OF DISTURBANCES IN MATERNAL-INFANT INTERACTION TO THE DEVELOPMENT OF PSYCHOPATHOLOGY IN THE BRAIN-DAMAGED CHILD

Prevailing psychiatric concepts hold that "traumatic" experiences during infancy tend to condition the development of emotional disturbances in later life. It is believed that long-term character trends begin to operate in early life and that the maternal-infant interaction contributes to the development of these trends. In infants with defect or damage of the central nervous system, the nervous pathways on which normal maternal-infant relationships depend are frequently affected to such an extent that pleasant reciprocal experiences are impossible and are replaced by a series of unpleasant associations. Thus emotional disturbances may become an integral part of the disease.

Benedek[2] refers to the early maternal-infant relationship as a symbiotic one in which there is reciprocal responsiveness. In order to function adequately, a mother requires an infant who is responsive to her care. When the infant is unresponsive or responds inappropriately to the "cues" supplied by the mother, her responses in turn may become inappropriate, and the symbiotic relationship is disrupted, producing a chain-type of reaction.

Among the occurrences which tend to initiate disruption in the maternal-infant symbiosis are feeding disturbances which result from the poor sucking and regurgitation to which many affected infants are predisposed. In spite of adequate maternal care and competence the infant often feeds poorly and fails to respond appropriately to the ministrations of the mother. In this instance the reciprocal mechanism from the infant is impaired, maternal care is affected, and the feeding situation, as representative of the basic elements in the maternal-infant relationship which are essential to early psychologic development, is disturbed.

Perlstein[12] has referred to the frequency with which colic is seen in early life in severely damaged infants with cerebral palsy. Colic may be interpreted to mean excessive crying which continues in the presence of the mother, and it is thought to be indicative of failure of the maternal-infant relationship to provide comfort for the infant. Colic also tends to disturb the maternal-infant symbiosis in a reciprocal manner, and a

mother becomes less capable of meeting the baby's needs when her best previous efforts have met with failure and she has become fatigued.

In an affected infant colic may be the result of the disrupting effect of the neurologic disturbances on the maternal-infant relationship which causes the infant to become relatively defenseless against uncomfortable sensations. Evidence for this is derived from the fact that sensory and perceptive difficulties are frequently discovered during the course of psychometric studies of older children with defect or damage of the central nervous system.[4] It is reasonable to assume that these disturbances, acting at an earlier age, may influence the capacity of the infant to interpret environmental stimuli in the usual manner. Thus sensory and perceptive disorders may impair the routes by which a mother normally communicates comfort to her infant, and perceptive distortion may lead to the enhancement of unpleasant stimuli. Such an infant would not be comforted by the mother's presence and would experience prolonged discomfort and anxiety.

In a sense, severe neurologic dysfunction in the sensory and perceptive area may result in such a disruption of the usual avenues of communication between mother and infant that the infant is in effect wholly or partially isolated from maternal contact. As a consequence, the infant may experience the equivalent of a degree of maternal deprivation. The resultant psychologic effects are sufficient in the normal infant to impair physical, neuromuscular, emotional, intellectual and social growth.[3] In the infant with neurologic disturbance they may provide an added handicap with effects indistinguishable from those of the neurologic disease. The prevalence of autistic traits among affected children is suggestive of the results of maternal deprivation and impairment of the formation of object relationships. At times autistic behavior is sufficiently pronounced in the brain-damaged child to cause diagnostic confusion with the syndrome of infantile autism.[6]

Disturbances in timing in maternal-infant relationships are likely to continue for the affected child, and one difficulty may lead to another as the influence of early disturbances affects subsequent levels of personality formation. In the second year of life delay in the acquisition of motor skills, with or without obvious disturbance in motor function, may interfere with the development of sphincter control and opportunities for independent activity. Delay in the development of verbal ability further retards autonomous behavior.

PSYCHOLOGIC PROBLEMS OF PARENTS AND CHILD

The occurrence of defect or damage of the central nervous system in a child is a difficult realistic problem which is likely to be life-long and for which there is little hope of complete recovery. The most that

can be expected of the prolonged application of professional skills to the management of the problem usually is some degree of improvement within the limitations imposed by the basic organic involvement. Such a problem places heavy demands on the capacities of parents and produces feelings and reactions which are important factors in the lives of the parents and the child. In the majority of instances the lives of both the parents and the child tend to be adversely affected. Thus the focus of interest should center about the family unit.

Once defect or damage of the central nervous system is identified, parents do not feel toward the affected child as they would toward a normal child. How profoundly parental feelings are altered influences the extent to which healthy relations are present or absent for the child. Some parental feelings may be symptomatic of unsatisfactory adaptation to the disorder and may tend to impair effective integration of the problem into the daily life of the family.

Acceptance is a term which is often used, but which does not adequately describe the process of adaptation of parents to a defective child. Parents probably never succeed in arriving at a complete acceptance of the problem, and a handicapped child does not present a single problem for which there is a single or final solution. Problems continually arise at different developmental stages as the full extent of the process unfolds. A *series* of social and psychologic adaptations is necessary, and the effectiveness of the adaptations can be measured by the extent to which the needs and capacities of the child and of the parents are fulfilled simultaneously under the circumstances of the disease.

PARENTAL REACTIONS TO THE DIAGNOSIS

Kirk[10] describes the reactions of parents to a diagnosis of defectiveness in the child under the following headings: shock, disbelief, fear and frustration, and intelligent inquiry.

Shock and Disbelief. The immediate impact of diagnosis is profound for most parents, and the reaction is often characterized by partial recognition alternating with attempts at denial. In a sense this stage indicates a preoccupation of the parent with his own feelings, and its duration depends in part upon the emotional resources of the parents, their degree of maturity and the availability of guidance. It may last for days or weeks or, in some instances, for years. Parents who are unable to effect a satisfactory initial adaptation to the problem may persist in denial in spite of adequate professional help as evidenced by ill-conceived trips to various physicians, clinics, cultists, and so on, in the hope that someone will reverse the diagnosis or offer a magic cure. Persistent denial reflects a significant incapacity of the parents to inte-

grate the problem into their life situation and indicates a lack of the most basic adjustment necessary to constructive planning.

Fear and Frustration. At this stage the parents recognize the existence of the problem and no longer attempt to deny it. This is a stage of disorganized fear, and feelings are often too intense and poorly defined to permit a rational or systematic approach to the problem. Consequently it is not a stage in which parents can react appropriately to the needs of the child. Fears about the future with relation to outcome, care, facilities, institutionalization, finances, and the like, may be overwhelming. Feelings of guilt and self-recrimination often predominate, and marital discord may be intensified. Many feelings are present which the parents need to discuss; the physician's interest and objectivity at this stage offer support and guidance for the development of an adaptation which can facilitate realistic planning.

Intelligent Inquiry and Planning. At this stage parents have reached a workable adaptation to the problem. Their feelings may not be the same as those of a parent for a normal child, and the situation may not be ideal for the psychologic development of the child; nevertheless the parent can react to the child constructively and meet some of the child's needs. Parents may arrive at this stage spontaneously as a result of a capacity to adapt and mature after a sufficient passage of time. In many instances, however, a considerable amount of professional guidance is necessary. Many parents never reach this stage or arrive at it after an unfortunate lapse of time which might have been utilized effectively for their own and the child's benefit.

Other Parental Problems

Problems which may arise are as numerous as the people involved. Some of the common problems are discussed in the succeeding paragraphs.

Guilt Feelings. No matter how intelligent a parent may be, irrational guilt feelings are usually present and affect the behavior of the parents. Such feelings may be responsible for self-sacrificial devotion to the child or excessive protection. Prolonged depressive reactions may reflect an incapacity to deal constructively with feelings of guilt.

Marital Adjustments. Marital adjustments which may have been tenuous before the recognition of the problem may become completely impossible afterward. At times guilt feelings of one parent may be projected onto the marital partner in the form of blame. Failure to have additional children is a common characteristic of parents of defective children and is often symptomatic of unresolved guilt feelings. In some instances elaborate precautions may be taken to avoid further pregnancies, or sexual intercourse may be avoided entirely.

DEFECTIVE CHILD AS PROJECTION OF PARENTAL IMAGE. Parents view their children to some extent as a projection of their own image. When the child is defective, the parent's feelings of self-esteem tend to be affected and influence the capacity to adapt unreservedly to the child.

AMBIVALENT FEELINGS. Parents of children with defect or damage of the central nervous system frequently have hostile feelings for the child which are close to the surface and often quite conscious. Consequently it may be difficult for them to provide consistency in the environment of the child. Parental reactions tend to vacillate between hostile attitudes at one time and compensatory feelings of guilt with overindulgence and excessive protection at other times. As a result, the parent often is unable to place disciplinary limits on one occasion, but is overrestrictive or punitive on another. The handicapped child, who needs consistency in his emotional environment, thus is exposed to more than the usual degree of inconsistency.

REJECTION. Confinement of the child or excessive punitive measures are symptomatic of complete rejection of the defective child by parents who are unable to integrate the problem. Less pronounced feelings of rejection are common among parents and alternate with compensatory feelings of guilt and indulgence.

INFANTILIZATION OF THE CHILD. Many defective children appear to be infantilized. Delayed speech, motor impairment and mental retardation are realistic reasons for failure to develop independence in self-care. Often, however, the parent continues to care for the child after the capacity for self-care is present. Overprotection arising from guilt feelings may contribute to this, but some parents infantilize the child in an attempt to keep him young and to deny thereby the reality of problems associated with growth and physical maturity.

AGGRESSIVE ACTIVITY. Parents may be unable to tolerate aggressive or hostile behavior in the defective child. Often as a result of motor disability, verbal limitation, restricted social outlets for play, and intolerance of parents for such behavior, all avenues for the expression of aggressive feelings are closed to the child. Many children, therefore, withdraw and spend long hours daily viewing television or engaged in passive and inhibited activity.

SEXUAL DEVELOPMENT. Masturbatory activity, the development of puberal changes, or evidence of developing sexual interest may be upsetting to parents of defective children. Such occurrences may arouse guilt feelings and fears which parents have regarding the role of their own sexual activities in the development of abnormality in the child. Parents also may have a fear of social and sexual delinquency in the child.

SOCIAL ISOLATION. With increasing age the child is likely to experi-

ence progressive social isolation and become more dependent upon the parents rather than less so. As a result, parental functions continue far beyond the usual point of termination, and the parent may find himself attempting to fill an impossible number of roles for the child in addition to that of parent. Often this prolonged dependency increases the ambivalence of the parent for the child.

PROBLEMS OF THE CHILD

The child who has severe defect or damage of the central nervous system may be unable to experience comfort and normal feelings in early infancy. Later he may be affected by inconsistency, hostility, rejection, overprotection and many detrimental influences symptomatic of the adjustment of the parents to the problem. Because of the child's difficulties in acquiring motor skills, developing independence, learning from experience, perceiving appropriately, and conceptualizing, behavior is often aberrant and tends to arouse antagonism or enforced isolation. The parents have not been prepared by their past experience to respond with understanding to this behavior. Eventually the child is likely to experience progressive restriction in social contacts, inadequate training facilities, difficult community attitudes, and limited opportunities for employment and recreation. Innumerable influences in the life of the defective child, therefore, tend to create psychologic disturbance. Ultimately intellectual and social limitations may make it impossible for the defective person to find a solution to conflicts between his instinctual needs and conscience. Neurosis, psychosis or psychosomatic disease may result.

MANAGEMENT

Therapeutic Goals

Management is directed toward the parents and the child with objectives for each.

For *parents* the objectives are (1) an early adaptation which permits the parent to meet his own needs as fully as possible while responding appropriately to the needs of the child, and (2) satisfaction in contributing in every possible way to the development of the child's fullest potentialities.

For the *child* the objective is a degree of social adequacy characterized by (1) as much self-sufficiency as possible, (2) productive use of capacities, and (3) happiness. Social inadequacy is characterized by the opposites and is often exemplified by institutionalization.

The Physician's Role

The physician contributes in the following ways to the management of the child: (1) diagnosis, (2) knowledge of resources, (3) continuing family contact, (4) good physical care.

The physician is usually the first to assess the affected child. The sensitivity with which he deals with the family may have a profound effect upon the processes of adaptation, and his manner may be interpreted as reflecting community attitudes. He may feel threatened by a lack of familiarity with the problem, an inability to provide an exact etiologic diagnosis, or more importantly by the fact that he cannot provide a specific cure. As the one who has the initial contact with the family, however, the physician should know the sources of help and referral within the community and state and should be able to initiate the program of assessment and management of the child.

Problems involving defect or damage of the central nervous system belong in the category of multiple discipline diseases, and as one of a group of interested professional persons, the physician need not feel personally inadequate if he does not possess the information necessary for the management of all aspects of the problem. The physician usually has a knowledge of the family based on continuing contact and may be the only one capable of seeing the child and the parents in their totality. Because of his biologic, social and cultural orientation, in addition, he is in a unique position to offer guidance to the family. Guidance is possible when physicians become comfortable in dealing with the feelings of people in association with illness and enlarge the scope of their responsibility. Under any circumstances medical abandonment or rejection, particularly by a physician whom the parents have trusted, may intensify the problem for the parents.

At best the problem is likely to be time-consuming. The child may be difficult to examine and "uncooperative," and the parents may have many difficult problems for discussion. Office care can introduce difficulties which interfere with the development of an effective relationship between parents and physician. The child may react poorly to a strange environment, the parents may be anxious about the child's behavior in the office, and the physician may be disturbed by the delay and disruption of his appointment schedule. If the child can be examined at home, many of the difficulties can be eliminated. Furthermore, developmental assessment is aided by observation of the child in familiar suroundings, family interactions can be observed, and discussion is facilitated in the relative relaxation of the home atmosphere. Guidance discussions with the parents, of course, can be scheduled in the office without the child's presence.

If the physician provides good physical care and does not resent

being called to treat the child, he may contribute a great sense of comfort to the parents. Death wishes for the defective child may be mobilized by an illness, and the parent may experience intense anxiety in attempting to interpret the severity of disease or to treat it alone. The physician's acceptance of responsibility for treatment provides a sense of security for parents.

In his relations with the parents the physician may be the object of projected parental feelings. Parents may blame the physician who delivers a defective child or establishes a diagnosis, or in various ways project their guilt feelings onto the physician. Under these circumstances great understanding and forbearance are necessary on the part of the physician to avoid retaliation.

Diagnosis. Recognition of difficulty is the starting point for planning. The acuity with which difficulty is recognized and the sensitivity with which it is discussed by the physician tend to lay the foundations of physician-parent rapport and to affect the course of parental adaptation.

Except for specific syndromes, the majority of instances of defect or damage of congenital origin cannot be diagnosed as specific entities, and only a functional evaluation is possible. Aside from the desirability of knowing the likelihood of progression, a functional evaluation of the neurologic disturbances is the only information essential for planning.

It is important for parents to feel that their problem has received adequate medical consideration if they are to rely on medical judgments. When special assessments are required, competent consultations should be obtained, and diagnostic measures should be performed for specific purposes with a knowledge of their limitations. Unrealistic attitudes toward laboratory procedures, particularly with regard to the etiologic information to be obtained or to possible therapeutic results, can be minimized if the physician himself does not have unrealistic expectations and if the parents are provided with an explanation of the purpose of the procedure. The physician must exercise caution to avoid being forced into a procedure involving some hazard by parents who consciously or unconsciously may hope for a fatal outcome.

Frequently it is impossible to assess a child's problem adequately on the basis of a single contact. Multiple contacts over a period of time are often needed before a comprehensive evaluation can be made. During the time when an evaluation is being formed, parents gain support from the wisdom, sense of direction and continuing interest of the physician.

Prognosis. A full discussion of all the prognostic implications at the outset would be overwhelming. In the beginning it is enough for parents to adjust to the immediate impact of the diagnosis. Thereafter

time is an important factor for compensation by the child, adaptation by the parents, and evaluation by the physician. It is best, therefore, to evaluate a child repeatedly, to avoid long-term forecasts, and to limit discussion to short-term aspects in keeping with the age of the child, environment, and community facilities. The capacity for change and compensation for defects or damage is often great in early life, and many variable and changing factors are involved in the outlook for any given patient. Only after the progress of the child has permitted a projection into the future and the parents have made a workable adaptation to the problem can an ultimate prognosis be of any help to those involved.

INFORMING THE PARENTS. Both parents should be present at the time the defect is brought to the attention of the family. The physician's explanation should be brief and simple, and only the immediate questions troubling the parents should be answered. A prolonged, one-sided discussion at this time precludes questions and reflects the physician's identification with the parents and his own anxiety in facing the problem. An appointment should be given in the near future for a more extensive discussion when the parents are able to formulate their questions and to articulate their feelings more effectively. Subsequent visits should involve the parents singly and together.

GUIDANCE AND COUNSELLING. Guidance at the practice level provides parents with an opportunity to share anxiety and to discuss feelings and problems in an atmosphere lacking in reproach, criticism or judgment. In the process of sharing anxiety with a professional person, its intensity is usually reduced. Parents are not usually looking for dogmatic advice in connection with their problems, and most of them realize that such advice is not practical. Problems relating to further pregnancies, moving nearer facilities, neighborhood difficulties, institutionalization, sibling relationships, and the like, require individual solutions. The physician should be oriented toward helping the family to work *through* these problems rather than toward minimizing them.

Discussions are confined largely to the feelings, anxieties and problems which parents express spontaneously. Thus the topics of discussion remain appropriate to the needs, and the physician usually is most effective if he avoids areas which are not immediately troubling parents. The physician generally does not give advice, but helps the parents to view problems realistically. Through discussion parents often can define their problems with increased clarity and arrive at personal solutions which are workable and appropriate to their specific needs. In time many parental guilt and depressive feelings can be resolved in such discussions, permitting finally an effective adaptation to the situation.

The physician should attempt to avoid judgmental or prejudicial

attitudes based on his own cultural background or fixed medical attitudes prevalent during his training. An example of the latter is the belief many physicians hold that institutionalization of a defective child is mandatory if there are normal children in the home.

For help with specific counselling and planning the physician can consult local professional sources, state departments of health, national organizations and directories of special facilities.

Other Professional Disciplines. Many different disciplines make contributions to the child as a result of their special interests. A few of the individuals and agencies who may become involved in the problem are the physician, psychologist, social case worker, speech and hearing therapist, ophthalmologist, orthopedist, physiatrist, adoptive agency, psychiatrist, educator, visiting nurse, sheltered workshop director, recreation director, employer, institutional director.

It is unrealistic to expect that the private physician has the training or the time to function in all these capacities. Therefore he must direct the patient to appropriate help when it is indicated. Often the various professional persons listed do not reside in the same community. It is important that the physician accept the responsibility of family guidance, therefore, and over-all coordination of management.

Community Resources

A mature parental reaction to the problem of the defective child involves confidence in the community that the child's interests and welfare will not be neglected. Many parents have a lingering fear of the fate of the child when they can no longer meet his needs or provide protection. To have faith in the community's acceptance of the problem, however, parents must have concrete evidence that it is warranted. This often is not so, and lack of community resources has a profound bearing on parental adaptation to the disease. Ultimately the possibility of the child's development of social adequacy is heavily dependent upon the available facilities for training and opportunities for social contacts.

Many of the community resources can be used in common by children with a variety of handicaps. An ideal community program might include the following facilities and services: medical facilities for early diagnosis, evaluation and care; psychologic evaluation; home training by visiting nurse, social case worker or preschool teacher; social case work; homemaker or baby sitting service; special educational facilities; special recreational facilities; occupational training and counselling; sheltered workshop or employment opportunities; psychiatric facilities; residential training when necessary.

Education and Training

It is not enough to provide education or training for the defective child of the same type as is provided for the normal child. Such children do not benefit from more teaching of a conventional type, but must have their needs met through special techniques. "Exceptional children" is the inclusive term applied by educators to the group of children of all types with special educational needs. Owing to teacher shortages, educational systems generally are reluctant to accept the responsibility of educating defective children, and many private facilities function with inadequately trained personnel. For available training facilities throughout the country the physician may consult the following reference source: *Directory for Exceptional Children: Schools, Services, Other Facilities*, 2nd ed., Porter Sargent, Boston, 1956.

Psychotherapy

As previously discussed, defective children often have severe psychiatric problems which interfere with social adequacy. There have been scattered psychiatric reports for many years of the beneficial effects of psychotherapy in these patients.[16] Sarason[14] states that except perhaps in the case of the most severely involved child, affected children appear to have feelings, needs, expectations, motives, and that they respond differentially to love and hate, reward and punishment, acceptance and isolation. Even mentally subnormal children appear to be reached by psychiatric techniques appropriately applied at a simple level. Systematic psychiatric studies have not been done in this group of children, however, and except for research investigations, wide-scale use of psychotherapy at present is impossible because of the inadequate numbers of trained psychiatrists.

When the physician observes parental reactions which are not being resolved with successful adaptation to the problem, he should attempt to help the parent to recognize the need for psychotherapy.

Parent Organizations

In order to function constructively when faced with adversity, every human being needs *hope*. Parent organizations provide hope as well as an opportunity for parents to share anxiety and to gain strength from identification with a group. In joining such organizations parents usually hope to better the care of their child by improving services through group action. Parents also view research as a symbol of hope, and fund-raising campaigns by parent organizations for research in specific diseases are psychologically important to parents for this reason. Paren-

thetically, it may be stated that the physician himself, personifying both service and research in medicine, also is a symbol of hope for parents.

Parent organizations are often not harmonious or unified. They may be dominated by individuals who, unable to cope adequately with the problems of their child, attempt to compensate by intensive activities in the community. Parent organizations, however, provide a means for organized action on a local and national level, and there are many tangible evidences of the beneficial results of their work. It is well, therefore, for the physician to keep in mind—even though he may not be in full agreement with their program or activities—that these organizations tend to fulfill a unique need in the psychological economy of the parents.

Institutionalization

In the past, institutionalization was recommended as soon as defectiveness was recognized in the child and often before adequate prognostication was possible. In many instances the mother was prevented from seeing or experiencing any relationship with the infant after birth, and direct institutionalization was advised. Inasmuch as institutional care was largely custodial in type, the affected infant or young child was often deprived of maternal care at an early age by this approach. The resultant psychologic effects of maternal deprivation have been sufficient in the normal infant to impair physical, neuromuscular, emotional, intellectual and social growth, for which Bowlby[3] has cited the evidence. In the defective child the results of maternal deprivation are probably indistinguishable from the neurologic disease and, when added to the basic handicap, tend to foster social inadequacy.

Currently the attitude toward institutionalization has changed. The economic burden of lifelong institutionalization is prohibitive, and emphasis has shifted to the home care of defective children whenever possible. Recently Beaven[1] has even made a plea for the adoption of subnormal children under suitable circumstances. Within institutions attempts now are being made, utilizing all available knowledge and skill, to habilitate affected children and to help them become socially adequate.

Tarjan[15] has made two helpful recommendations regarding the indication and procedure for institutionalization:

1. The need for institutionalization is determined by the condition of the child in relation to the ability of the parents, emotionally and physically, to provide the care that is needed.

2. Well-timed, voluntary commitment with parental consent and careful protection of civil rights is the best method of entry for most

children. Court commitment is unnecessary and can be an extremely traumatic experience for parents.

The decision about the care of the child should be a parental one made when the parents have had an adequate opportunity to resolve their feelings toward the child. The physician may counsel to the extent of giving a justifiable appraisal of the child to the parents and indicating the possibilities for care.

SUMMARY

Psychologic problems are an integral part of the symptomatology of children with defect or damage of the central nervous system and are a result of the disrupting effect of neurologic dysfunction on interpersonal relationships. Parents probably never succeed in arriving at a complete acceptance of the child's handicap; instead, a series of social and psychologic adaptations is necessary at different developmental stages. The physician's approach to management and the status of community resources may have a profound bearing on the integrative capacity of the child and the parents to deal with the problem. Ultimately psychologic difficulties are often the determining factor between social adequacy and inadequacy, which is the final criterion of the success of management of the affected child.

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CHARACTERISTICS AND MANAGEMENT OF CHILDREN WITH BEHAVIOR PROBLEMS ASSOCIATED WITH ORGANIC BRAIN DAMAGE

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Current interest in behavior disorders of childhood associated with brain damage is attested by the growing medical literature on the subject. Moreover, in nonmedical circles, teachers, psychologists and social workers have become very much aware of the "brain-injured" child, and as a result the family physician is being asked for his opinion regarding such youngsters with increasing frequency.

The present interest in the subject may reflect an actual increased incidence of brain-injuried children as more and more infants survive some of the potential hazards of prenatal life, childbirth and infancy. Moreover, the field of child psychiatry, heretofore largely preoccupied almost exclusively with the psychodynamics of children's problems, is now giving greater cognizance to physical factors in their genesis. These factors, coupled with a sizeable series of reports correlating behavior problems with preceding illness or injury in early life and with specific methods of clinical study, such as electroencephalography and psychological testing, are dealt with in recent reviews by Silver,[11] Bender,[1] Bradley[4] and Eisenberg.[6, 7]

BASIC CONCEPTS

Though not all children who survive illness or injury which might produce cerebral trauma are actually subsequently handicapped by

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sequelae of such experiences, a significant number come to later clinical attention. Some of these present problems almost exclusively in the area of behavior and social adjustment. In others the picture may be complicated by one or a combination of several syndromes, including various degrees of mental retardation, cerebral palsy, convulsive disorder or special sensory defect. This report deals with children whose basic problems are those of behavior without these additional complications. This group may particularly puzzle the physician because of the very absence of more familiar and conventional evidences of central nervous system damage.

Clinical experience indicates that the majority of children with behavior problems due to brain injury experience their trauma early in life—during the prenatal period, in association with the birth process, or during the first two or three years of infancy. The basic behavior difficulties of most of these children bear a striking resemblance to one another. With due allowance for the occasional special handicap which reflects damage to a certain localized area within the brain, the over-all effect of early cerebral trauma is that of disorganization. The special behavior characteristics of the brain-injured child which particularly distinguish him from his more fortunate siblings and schoolmates appear to be symptoms of weakened controls and diminished powers of inhibition. These direct evidences of the brain damage itself may be considered the *primary symptoms* of this particular category of behavior problem.

Human behavior is complex, however, and no pattern of adjustment in daily life is solely the result of any single factor. In addition to his primary symptoms, the brain-injured child shows behavior which reflects his feelings about himself, his adequacy and the special problems which his handicaps create for him, as well as his reactions to the way other people deal with him. These aspects of his behavior, so far as they contribute to the "problem" area of his general adjustment, may be termed his *secondary symptoms*.

The physician's problem, when parents bring the poorly adjusted brain-injured child to him, is to distinguish what is primary, and therefore of diagnostic value, what is secondary, and therefore of clinical importance, and what are quite unrelated complaints, and on the basis of his total evaluation to initiate proper remedial measures.

CHARACTERISTIC BEHAVIOR

Primary Symptoms

Puzzled and frustrated parents will of course describe their children's behavior difficulties in a variety of ways and in many different terms. The physician must cull from the welter of complaints and anecdotes

the material which is of clinical importance. In the majority of brain-injured children he will be able to distinguish a characteristic cluster of behavior symptoms which in their totality as a syndrome strongly suggest brain injury. No one of these symptoms is by itself of particular diagnostic significance. When they occur together as a group of behavior characteristics which distinguish the brain-injured child from others in his family and from most of his schoolmates, they reflect the disorganization and weakened controls which are the hallmark of behavior problems due to brain injury. The most important individual symptoms which make up this syndrome may be listed as follows: (*a*) unpredictable variation in behavior, (*b*) hyperactivity, (*c*) distractibility or short attention span, (*d*) impulsiveness, (*e*) irritability, (*f*) difficulties in abstract thinking, particularly in terms of number concept.

Unpredictable Variability in Behavior. Variability is what the parent or teachers observes when the child's mood and manner of adjustment are quite different at certain periods from what is observed at other times. The parent may speak of "good days and bad days." The teacher may report excellent retention of school material at one time and apparent lack of familiarity with it at other times. In contrast to most children, whose variations can be accounted for by preceding events which have recently occurred, the brain-injured child shows no logical pattern. His variations are conspicuously unpredictable and unexpected, both to himself and to those about him.

Hyperactivity. This may also be described as hyperkinesis, restlessness or agitation. The child who "runs and never walks," who "constantly wanders about the schoolroom," or who must "always be busy at something," is showing behavior of this sort, particularly when it is in contrast with that of other children of the same age.

Distractibility. This is probably synonomous with "short attention span" and is particularly noticeable in the classroom. It has been suggested that children who are distractible are "trying to pay attention to everything at once." The parent may note that the child never keeps constructively busy for any long periods of time, but constantly flits from one interest to another. The teacher frequently states that "he would do well in school if he would only pay attention long enough."

Impulsiveness. This refers to the characteristics of the child who "acts first and thinks afterwards" or who darts from one interest to another. His enthusiasms may be intense but evanescent and transitory, often reflecting the variability noted above.

Irritability. Irritability suggests ready excitability. This is particularly noted when frustrating situations are encountered. The child may react to these in an "all or none" fashion, with intense explosive behavior, probably most conspicuous clinically when it involves manifestations of rage and temper. In adults this type of reaction has been

termed "catastrophic," the person reacting to relatively minor irritations as though they were of immense and devastating importance.

Difficulties in Abstract Thinking. Such difficulties are probably most obvious in children of school age and in the school situation. Arithmetic is commonly the subject which is most difficult. Even in younger children poor concepts of number and quantitative values may be apparent. In older children, grasping the significance of what they read in print, abstracting information and drawing logical conclusions may present peculiar difficulties.

Secondary Symptoms

In contrast to the primary behavior characteristics of most brain-injured children, which bear a general similarity to one another from case to case, the secondary symptoms are as diverse and scattered as all human behavior itself. As noted above, they reflect the way the child feels about himself, the way he reacts to the disabilities imposed by his brain injury and the behavior characteristics noted, and are to a large extent influenced by the way other persons deal with the child. Moreover, these secondary manifestations may be conditioned by his basic personality characteristics (whether he be aggressive, passive, withdrawn), by his age and development, by the presence or absence of other sequelae of brain injury, or indeed by any other assets or liabilities. Among the more frequent and conspicuous of the secondary symptoms are the following:

Anxiety. This has been termed "fear without a focus" and indicates vague, pervasive worry or uneasiness related to a wide variety of situations in which the child may find himself. The fact that he is "different" from other children or has special problems which he does not understand can explain this symptom in some children. Also the fact that a child cannot rely on himself because of the unpredictability of his own behavior is often another contributory cause. It is easy to understand why the erratic, explosive behavior of many brain-injured children provokes anxiety in their parents and teachers. In turn, the children are sensitive to these feelings in the adults and, as a result, feel more anxious themselves. The psychopathology of anxiety in brain-injured children, as well as the more complex aspects of other primary and secondary behavior symptoms, is discussed in more detail elsewhere.[1, 4, 6, 7, 11]

Emotional Immaturity. This implies that a child appears to react with behavior which would have been more appropriate at an earlier age period. The parents may describe this in various ways, among them noting that the child appears "self-centered" or "selfish." It has been suggested that the feeling of being "different" from other children tends

to focus a child's attention on his own wishes and needs. Likewise the handicaps imposed by brain injury often hinder children from achieving success and satisfaction in the various developmental stages through which they must pass as they progressively develop a mature and well rounded personality. This favors the retention of some more childish characteristics than are appropriate. Moreover, the tendency of all children to revert to earlier behavior patterns in the face of frustration contributes to the clinical impression of immaturity in certain youngsters.

Compensatory Mechanisms. Compensatory mechanisms, such as negativism, stubbornness, refusal to obey commands, boasting of fancied accomplishments or bullying younger children, all represent the way children may react to their disabilities and attempt to boost their egos and control their environment in self-defense.

Delinquency. Delinquency, which may be defined as "breaking the law and being caught," though not necessarily conspicuous in many brain-injured children, may occur as a compensatory reaction. Some children feel guilty because of the ceaseless criticism which their unacceptable behavior brings them and may unconsciously seek punishment for themselves by committing acts for which they will presumably be caught and chastised. Much delinquency occurs as the result of frustration, and many brain-injured children become frustrated.

School Failure. This is not surprising in children whose personalities are characterized by the primary symptoms noted previously. Distractibility and poor power of concentration preclude academic success, quite apart from the social obstacles they present to a good adjustment in a busy classroom.

General Personality Patterns. Each child has his own general way of meeting problems quite apart from those aspects of behavior which are the result of brain injury or other special complication. These basic patterns are determined by a complexity of factors which cannot be adequately discussed here. Tendencies to passive withdrawal from difficult problems on the one hand, or, in contrast, aggressive reaction to challenging situations on the other, inability to have confidence in, identify with, or give affection to others, are random examples of general patterns which characterize some children. Some of these patterns may become apparent early in life and certainly color the impression a child may give to those who live with him. These impressions may be so conspicuous as partially to obscure those aspects of brain-injured children's difficulties which stem from their special handicap. This may make it difficult for the clinician to recognize the "primary symptoms" which have been described and lead him to suspect that there is very little which really distinguishes the brain-injured child from children with other sorts of problems. In such instances the use of additional diagnostic aids may clarify his focus.

DIAGNOSTIC AIDS

It is obvious that no diagnostic label adequately describes or explains the total life adjustment of any child. Careful evaluation of the special behavior characteristics of children with brain damage may, however, lead the clinician to an appreciation of what may be contributing to their special problems. For more complete and accurate diagnosis, information in individual cases may be available from one or more of the following sources, to which space permits only the barest allusion: (*a*) psychological test performance, (*b*) a positive history of presumptive cause of brain injury, (*c*) neurological examination, (*d*) special diagnostic tests such as the electroencephalogram.

Psychological Test Performance

This is of considerable diagnostic assistance if testing is carried out by an experienced clinical psychologist who is alert to cerebral trauma as a possible factor in behavior disorders.[8, 13, 14] The total score or intelligence quotient as determined on conventional children's tests may not be revealing, particularly in children in whom mental retardation or specific neurological defect are not complications. However, a child's performance on selected subtests and on certain special examinations, as well as the way he reacts in the testing situation, may indicate that organic factors are seriously influencing his adjustment. Space does not permit adequate discussion of these special techniques, but the physician will do well to avail himself of the services of a clinical psychologist if they are available.

A History of Illness or Injury

When illness or injury may have caused brain trauma, such a history is of course helpful when it is clear cut. Since, in many instances, the trauma may have occurred prenatally or under circumstances with which the mother is not entirely familiar, a positive history is not always available. Specific inquiry into the mother's health during pregnancy, conditions during birth itself and the child's health during the infancy period are particularly significant.

Neurological Examination

Neurological examination is helpful when positive findings are elicited, although their absence does not preclude brain injury, since the latter may be reflected in behavior alone. It has been suggested that in addition to the customary examination of tendon reflexes, coordina-

tion, and the like, attention to postural and righting reflexes may yield information of diagnostic significance.[1, 12]

Electroencephalography

The electroencephalogram has contributed a great deal to our understanding of central nervous system function and is of diagnostic value in many clinical disorders. The findings do not correlate directly, however, with specific behavior patterns, with intelligence or with the presence or absence of known antecedent trauma. As an adjunct source of information, combined with data obtained from other areas, it may be very useful.[5, 9] The same comments might be made about other special diagnostic procedures, such as the pneumoencephalogram or arteriography.

MANAGEMENT

Experienced workers largely agree that the outlook for the brain-injured child depends to a large extent upon the degree to which he is warmly accepted by his parents, the success which he experiences in school and in the community, and the satisfactions which he derives from daily life. These can all be facilitated by the physician, who should not be misled by the note of finality and pessimism which the cold term "brain injury" suggests. Efforts to promote a better adjustment and more successful life for the child may be profitably made in the following areas: (*a*) working with parents, (*b*) direct help for the child, (*c*) assistance in planning educational programs, (*d*) promoting understanding of brain-injured children in the community.

Working with Parents

It is not surprising that most parents of brain-injured children are puzzled, frustrated and anxious as the result of the unpredictable, explosive, erratic behavior of their youngsters. If the physician can recognize the problem, he is in a favorable position to eliminate some of the parents' misconceptions and confusion and assist them to help their youngsters.

The first step is to give a clear explanation of the child's problem. Both parents, together or individually, should hear this directly from the physician. If parents can understand and accept the concept that illness or injury contributed to a considerable extent to their child's difficulties, they may become better able to gain a more objective outlook on the various problems involved. An acceptance of the organic physical factors may give them some relief from feelings that they themselves are

entirely at fault. Many parents have been helped by reading material such as *The Other Child*, a book written by the parent of a brain-injured child with the collaboration of a physician.[10]

In addition to a fairly clear understanding of the nature of the child's difficulties and the significance of the primary and secondary symptoms, most parents need guidance in certain specific areas. The fact that the brain-injured child is "growing up the hard way" and will understandably be somewhat childish and immature in his reactions for some time to come makes it necessary that the parent deal with him as if he were a younger child. In the face of the barrage of unsolicited information contributed through mass media, which more often than not suggests that children "should be encouraged to have independence" and "should be allowed to grow up," most parents need their doctor's support in continuing to treat their brain-injured children as younger individuals and thereby try to meet their particular dependency needs. It is also obvious that the erratic, unpredictable child with brain injury has particular difficulty in controlling himself. The child may actually welcome the judicious use of positive guidance and discipline at the hands of parents and certainly needs it to direct his activities in a constructive fashion. Passive and patient understanding alone do not supply this. Whenever possible, practical suggestions for specially suitable activities for the child may also be a source of considerable help to harrassed parents.

If children's psychiatric clinic facilities are available, the physician may use them as a source of consultation or more extensive guidance than he feels he can provide in his own office. There are many areas of the country where such facilities are not directly available for frequent therapeutic contacts, and in many instances the physician himself must serve as the parents' guide.

Direct Help for Child

The family physician may be most helpful in counseling the child directly. If his contact is good and the child has confidence in him, his positive directions and objective understanding of the various complications involved may make him a resource whom the child will welcome. In addition to this highly personalized type of assistance, the physician may offer help through conventional medical channels.

Certain medications may be valuable adjuncts to promoting a child's social and scholastic success.[2] If, with the use of medication, the extremes of the child's primary behavior characteristics can be reduced and be made less frustrating and irritating to him, he may become "easier to live with." As a result, parents, teachers and other children may be able to give him greater acceptance and recognition. Medication is at best a crutch, but if in the long run it enables the child to

experience success and a sense of being loved and appreciated, its use is well justified.

For the promotion of longer attention span and better application to school work, as well as for reducing some of the variabilities that characterize the brain-injured child's pattern of adjustment, amphetamine sulfate and dextro-amphetamine sulfate still appear to be the drugs of first choice. Their use has been summarized elsewhere.[3] They should be used in adequate dosage (amphetamine sulfate, 10 to 20 mg. daily in the morning for children beyond the age of six years; dextro-amphetamine sulfate in approximately half that dosage). A morning dose is suggested to promote better adjustment during the school hours, to preclude sleep disturbances, and in most instances to give some assurance that later in the day the depressing effects on appetite may wear off before the evening meal.

For the relief of symptoms related to explosive, catastrophic reactions, some of the newer "tranquilizing" preparations may be of assistance. In the light of available established knowledge it appears that chlorpromazine in doses of 10 to 25 mg. two or three times a day in children beyond the age of six years is most likely to be of assistance. The slight hazard of undesirable complications may be weighed against the urgency of the child's social problems, which are often desperate. Reserpine preparations in doses of 0.1 to 0.25 mg. two or three times daily may also be used. Reports on the results of an ever-growing assortment of newer tranquilizers and muscle relaxant drugs, as applied to children's problems, are few and still hard to evaluate. Antihistaminic preparations have also been suggested.[2]

One might anticipate that some of the anticonvulsant drugs would be of particular assistance to brain-injured children. There are a few scattered reports to this effect in the literature of the past dozen years. Personal experience suggests that, though excellent for controlling or eliminating seizures themselves, such preparations do not have a striking effect on children's behavior. Occasionally diphenlhydantoin may result in a dramatic effect. Its freedom from serious side effects warrants in trial in doses of 0.1 gm. once or twice daily.

Barbiturates and other sedatives are generally contraindicated for the relief of children's behavior symptoms. Phenobarbital is particularly misused in this regard. In minimal doses it probably has no more than suggestive effect, which is not adequate for the urgent problems of children with brain damage. In larger doses it is likely to act as a stimulant for some children and to increase irritability and distractibility in others.

Medication is never a cure-all for the brain-injured child. If, for a year or two, it may promote better success in school, better acceptance in the community, and by so doing contribute to the child's feeling of self-sufficiency and confidence, its use is well justified. The more per-

sonal contact the physician can maintain with the child while prescribing for his medical needs, the more likely will be the successful outcome of his drug therapy.

Planning an Educational Program

As has been mentioned above, the brain-injured child is poorly equipped for rewarding school experiences. Special education programs are usually indicated. Most physicians are not in a position to supervise them directly or to supply details, but can be of considerable assistance in pointing out the nature of the child's disability to school personnel and assisting them in taking appropriate steps. The literature on specific educational methods which have proved successful with children who have suffered cerebral injury is scattered and diffuse, but the contributions of Strauss and his co-workers should be readily available as an initial source of reference to those who are most interested.[13, 14]

Small classes which permit a great deal of individual attention are usually desirable. Any steps which can be taken to cut down the likelihood of distractions in the classroom are important. One simple step in this direction is to have the brain-injured child carry out his school tasks at a desk which faces a corner or a wall or is located in a cubicle where the visual and auditory distracting stimuli are reduced to a minimum. The use of concrete materials in trying to teach abstract subjects, particularly those having to do with number concepts, should be seriously considered. It is probably helpful for the teacher to have some understanding of the effect any medication may be having on the child's behavior. Teachers as well as parents can be more objective when they understand the true nature of a child's difficulty, and the physician may often wisely make the proper interpretation to them if the parents so desire.

Promoting Awareness in the Community

Some community awareness of the fact that behavior disorders and disturbances may be related to physical illness is probably timely. The fact that brain-injured children are difficult to live with and that parents may understandably be frequently at their wits' end with their problems is information which probably can be wisely disseminated in a day when there is a tendency to attribute children's difficulties to the faults of their families. Though the physician is not in a position to discuss publicly the personal idiosyncrasies of his individual patients, he may be in a position, through parents and through school personnel, to promote public understanding of the problems of brain-injured children. It is often difficult to explain behavior difficulties without appearing to

make excuses for them, and a judicious combination of recommending firm controls and positive guidance, coupled with an understanding of basic underlying causes of children's difficulties, has much to recommend it. A useful service in some communities in the public interest is to promote the availability through public libraries of literature for parents and school personnel on special clinical topics such as the one under discussion.

PROGNOSIS

As has been indicated previously, experienced workers tend to agree that the outlook for the brain-injured child depends largely on the attitudes of those who deal with him and the success which he achieves in daily life and in his social contacts. These favorable factors can of course be promoted by the physician. In general the outlook for the brain-injured child is better than had previously been anticipated.

Additional factors which undoubtedly contribute to this, whether or not the child receives specific help, are, first, the fact that with increasing age maturity does contribute certain abilities for compensation and adaptation. Moreover, in our culture small children are expected to lead a much more stereotyped and prescribed life than we sometimes realize. They are expected to get up and go to bed at certain times, to eat their meals at prescribed periods and to partake of food which others select for them. They must attend school and behave in a reasonably conventional fashion while so doing. In adolescence and adult life these restrictions become somewhat lifted. The brain-injured child is poorly endowed to fit into any prescribed way of life, and possibly the greater latitude which he experiences as he grows up may contribute to his better adjustment as an adult and fully grown person in certain instances.

In spite of the favorable prognosis for many children, one cannot gainsay the seriousness of the problems the brain-injured child encounters. Every effort must be expended by the physician and those with whom he comes in contact to promote a more satisfactory way of life for such children and their families.

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THE STUDY OF THE EPILEPTIC CHILD

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Rapid advances in modern medicine make it increasingly difficult for busy physicians to keep abreast of recent developments. This is particularly true of the more complex diseases, of which epilepsy is an example. The need to have a somewhat detailed knowledge of this condition is borne out by the fact that approximately one in every 15 children has a convulsion at some time.[3] Therefore physicians dealing with children cannot avoid the problem of the child with seizures. Those who seek a better understanding of epilepsy will be richly rewarded in the greater security gained in the diagnostic approach to the child with convulsions and in the sounder knowledge of methods of treatment.

With the exception of monographs and textbook chapters on epilepsy, most papers on this subject deal with isolated aspects, such as drug therapy, surgical methods and electroencephalographic findings. Although definitive work-up of the epileptic patient is championed by all, few authors elaborate upon the details of the investigation.

It is the purpose of this paper to discuss in a simple and somewhat informal manner the comprehensive study of the epileptic child. Such a total approach includes many aspects other than the seizures themselves. It considers also the psychologic, physiologic, social and community aspects of the problem. It extends beyond the narrow limits of description of attacks and prescription of drugs. It focuses on the child with the disease, not the disease alone.

Our thinking will be clarified if we remember that a convulsion is merely a symptom and that many processes, some of them poorly understood, can cause this same symptom.[3, 4, 19, 20, 21] In every instance the first step is to seek the cause. Obviously some causes are correctable, and one works in the dark unless utmost attempts are made to uncover

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the etiology of the attacks. By etiology is meant definable disease processes or contributing abnormal physiologic and psychologic states that result in the convulsions. The basic mechanism of the seizure remains a mystery.

The general approach to epilepsy includes investigation of etiology, attempt to define the areas of the brain involved, classification of types of seizures, and methods of treatment. Keeping these points in mind will channel the diagnostic work-up.

ETIOLOGY

From the standpoint of etiology, one may visualize the convulsive seizure tendency as a reservoir impounded by a dam, which is the convulsive seizure threshhold. When the level of the reservoir exceeds the height of the dam, a convulsion ensues. Four "streams" flow into this reservoir: (1) hereditary tendency to seizures, (2) brain damage, (3) physiologic factors, (4) psychologic factors. The level of the reservoir can be raised by excessive flow from one or more of these streams to produce a convulsion.

In pediatric practice the stream that contributes most often to seizures is the one entitled "brain damage." Such injury may occur prenatally, perinatally or postnatally, and much of the history-taking in the epileptic child centers about these possibilities. By damage is meant injury to a brain whose normal growth and development was distorted by some adverse effect, or effects, acting at any time after conception. When such injury occurs early in embryologic or fetal development, the resulting deformity may be difficult to distinguish from genetically transmitted malformations.

Although it is true that occasionally one finds clear-cut evidence that the convulsions in the child are on an inherited basis, most epilepsy is not so determined, and one should be cautious in maligning genes.[18] Families already unhappy are not made happier by ill-founded allusions to tainted heredity as the cause of seizures in the child. Recent advances in technical methods of studying epileptic patients, and particularly full-scale assault on the diagnosis by all means available, more often prove that brain damage is the cause rather than heredity.

Physiologic factors may either serve as trigger mechanisms to increase the frequency of seizures, rather than directly causing them themselves, or they may be the sole cause of the convulsion. In the former class, for example, fall some patients whose excessive ingestion of water and food appears to initiate seizures to which they are already predisposed. In the latter class are included such entities as hypoglycemia and the various forms of tetany.

Psychologic maladjustment may serve as a trigger mechanism to

increase the frequency of seizures in children so disposed. Of course, maladjustment itself does not cause convulsions. Bridge[3] emphasized the importance of psychologic evaluation of the epileptic child, not only in order to understand him and his problem more fully, but also to correct maladjustment as a helpful step in therapy.

In the following discussion chief emphasis is given to the child with recurrent convulsive seizures, not to the patient who has only an isolated convulsion.

STUDY OUTLINE

With this introduction in mind, I would now like to take up, point by point, the outline for study of the epileptic child used in the Children's Convulsive Seizure Clinic of the Pediatric Division of the University of Tennessee. The outline, considered to be fairly comprehensive, includes many points that can be covered reasonably quickly and is not as complicated as it may seem. It is arranged with space for writing beneath each of the various headings, so that, when completed, an orderly evaluation of the problem is obtained.

The first section contains identifying data, such as the date, patient's name, age, race, sex, hospital unit number, and the name, address and telephone number of the parents. The name of the informant is given and whether the informant seems to be giving a reliable history.

The next section deals with possible etiologic factors. It includes the family history, prenatal record, perinatal factors and postnatal conditions that may have resulted in brain damage.

Family History

Under Family History one inquiries about convulsions in siblings, parents, grandparents, uncles and aunts. In view of the tendency for febrile convulsions to be on a hereditary basis, the specific question is asked whether convulsions of relatives were associated with fever or not.[6] Other questions about the family include history of mental deficiency or frank mental disease, conditions that suggest for the patient the possibility of a transmitted defect.

Prenatal Factors

There follows a consideration of prenatal factors that may have damaged the child's brain. Some of the questions asked in this section are based on the results of animal experimentation in which deformities of offspring were deliberately created by manipulating the pregnant animal's environment, food intake, and so forth, during gestation.[9, 16, 17, 25]

Not all these potentially adverse factors are known to act in human pregnancies, but some are believed to.[16, 24] Chief emphasis is given to factors acting in the first few months of gestation, the period of organogenesis in which malformations are more likely to occur.

In this section one inquiries about *vaginal bleeding and/or cramping*, which suggests, of course, that the placenta partially separated from the uterine wall and that the fetus may have suffered hypoxia. If bleeding or cramping occurred, information is obtained regarding time of onset and duration and whether the bleeding was mild, moderate or severe.

Questions are asked regarding *febrile illnesses during pregnancy*, with special emphasis on maternal viral infections early in gestation. It is widely known that if a woman contracts rubella early in pregnancy, there is a significant possibility of fetal damage, including microcephaly, deaf-mutism, cataracts and congenital heart disease. Other viral infections, however, may also cause fetal damage.[16] If the physician taking the history did not examine the mother during the infection, he may still be able to obtain data from the mother's physician or a hospital record that may suggest viral infection, such as respiratory symptoms accompanied by leukopenia.

The mother's *diet* during pregnancy is evaluated, and also whether she had *hyperemesis gravidarum*. Warkany produced malformations in the offspring of pregnant rats deprived of various nutrients, especially vitamins,[25] and some investigators feel that human offspring may also suffer deformities because of an inadequate maternal diet or severe vomiting.[24]

The next inquiry is directed toward *pelvic irradiation* during gestation, particularly early in the pregnancy. This has become a rarity since physicians have learned the importance of determining whether pregnancy exists before irradiating the pelvis of a woman in the child-bearing years, lest damage to the fetal brain occur.

Our next question may seem a bit unusual, but is based on the experiments of Ingalls,[16, 17] who created malformations in the offspring of pregnant mice subjected to hypoxia, and who believes that *high altitude flying* in inadequately pressurized planes may possibly cause brain damage to the fetus early in gestation. Naturally our charity patients rarely take plane flights, but more and more private patients are flying across oceans and continents, and some of the flights are at high altitudes. When I traveled recently through Mexico, Central America and South America, oxygen deprivation was evident on several of the flights across high mountains. If one considers the large number of tourists these days, and that some of them are pregnant, the possibility of fetal damage may be real. In a similar way it is thought that *trips to high mountains* when the mother is in the first trimester of pregnancy may be dangerous.[16]

We are interested in whether the mother had *hypertension* during the pregnancy, especially whether she had moderate to severe eclampsia, since eclampsia results in a higher stillbirth rate and liveborn babies of eclampsic mothers have less chance of survival than do infants born of normal mothers. The frequency with which eclampsia may result in fetal brain damage sufficient to produce subsequent convulsions is not known, but deserves further investigation. It is logical to suppose that generalized arteriolar spasm associated with eclampsia might result in decreased placental oxygenation which could, perhaps, produce fetal hypoxia.

It seems doubtful whether moderate degrees of *hypotension* during pregnancy would result in fetal hypoxia. It is known, however, and we ourselves have observed, that babies born of mothers whose blood pressure reaches markedly hypotensive levels during labor may suffer brain damage, presumably hypoxic.[13] Reference to this point will be made later in consideration of factors operating during labor.

Severe *anemia* during pregnancy is a point of interest since, if it is uncorrected, the mother enters labor and delivery with less oxygen-carrying capacity of her blood and therefore less margin of safety in regard to prevention of fetal hypoxia.

Cyanosis during pregnancy occurs only rarely, but since it implies diminished oxygen saturation, it carries the threat of fetal hypoxia, which could lead to brain damage. Perhaps the most interesting instance of this situation so far reported occurred in our hospital a few years ago and was reported by Olim and Turner.[22] The mother had the tetralogy of Fallot, and her blood had a constantly low oxygen saturation. Her first two pregnancies resulted in the birth of anencephalic infants. After a Blalock-Taussig operation her oxygen saturation rose to higher levels, and she then gave birth to two perfectly formed infants. One swallow does not make a summer, but at least this case seems to suggest clinical confirmation of experimental teratology.[17]

In taking the prenatal history one also inquires about possible adverse factors other than those discussed above. It is of interest *whether the mother was anesthetized* at any time during pregnancy, especially in the first trimester. This might have been done for minor elective surgical procedures, or even dental extraction. Properly performed anesthesia probably carries little risk to the fetus, but not all anesthesia is wisely planned and skillfully conducted. Again, the possibility of fetal hypoxia is the point of interest. The *operation* itself may have been a major one, and the condition of the mother may have been such that fetal damage might have occurred as a result of blood loss, shock or respiratory depression.

The role of *severe maternal illnesses* in fetal brain damage is not clearly elucidated. Bacterial infections are not ordinarily transmitted

across the placenta, but if the infection is of great severity, the baby may be miscarried or might conceivably suffer damage. We are also interested in such maternal illnesses as heart disease, chronic nephritis, diabetes mellitus, syphilis and toxoplasmosis.

Trauma to the abdomen may play an etiologic role in fetal brain damage if it causes cramping and bleeding which decreases oxygenation of the fetus.

Perinatal Factors

Numerous factors associated with labor and delivery may result in damage to the baby's brain. Such injuries usually result from intracranial hemorrhage or hypoxia, or combinations of the two. Anyone who has made a special study of the relationship of labor and delivery to fetal brain damage, as we have done,[11, 13, 14, 15] realizes the complexity of this situation. Certain factors easily identifiable are clearly related to fetal brain damage, but often combinations of adverse factors exist and interpretation is difficult. Another factor handicapping analysis of this relationship is the fact that most obstetric records are rather incomplete, from the unborn baby's standpoint, even in teaching hospitals. In most instances attention is still directed much more closely to the condition of the mother than to the possible hazards the fetus is experiencing.

With full realization of these numerous difficulties in collection and interpretation of data, our next section in the work-up of the epileptic child centers around perinatal factors.

One is interested in the *parity* of the mother, since firstborn babies have a greater chance of suffering brain damage because of the likelihood of more difficult labor.

We also wish to know *where the mother was delivered*, in order that her obstetric record may be analyzed if available, or an abstract of findings may be obtained if she was delivered in another hospital.

Labor and delivery are analyzed from the many standpoints that have a bearing on the likelihood of intracranial hemorrhage or fetal hypoxia, as indicated in the following paragraphs.

Interpretation of the *intensity* of labor is a difficult thing unless notes are being recorded as labor progresses. Tumultuous labor with unduly rapid progress of the baby's head through the birth canal may increase the hazard of trauma to the fetal brain.

Duration of labor is more easily ascertained, but here, again, there is some difficulty. Mothers giving histories of their labors often cannot say when real labor actually began, often confusing false labor with true labor.

Hemorrhage before birth of the baby suggests presence of placenta

praevia or premature separation of the placenta, either of which may cause fetal hypoxia and shock. One must distinguish between mere spotting of blood and copious bleeding. The obstetric record should be consulted.

Toxemia at time of labor can be identified more easily because of the associated hypertension, edema and albuminuria. Most women know whether they had these findings. Again, the mother's obstetric record should always be consulted in interpretation of the epileptic child.

The fetal presentation is of interest, since breech presentations, like transverse and other abnormal presentations, carry more hazard. Although intracranial hemorrhage and/or hypoxia may occur when babies are born by cesarean section, delivery by the vaginal route is generally more liable to be traumatic.

In questioning about use of *forceps*, one must distinguish between application of low forceps, often protective, and mid- or high forceps, less commonly used and more often associated with factors already pointing toward fetal brain damage. Unfortunately, the skill of the obstetrician in performing any of these maneuvers cannot be evaluated accurately from merely conversing with the mother or consulting her obstetric record.

Occasionally one obtains a history that, in "consideration of the mother," the baby's crowning head was held back until the details of the delivery could be properly arranged (physician not immediately available, and so on). This can lead to serious hypoxic damage to the baby's brain, eventuating in epilepsy or other evidence of neurologic injury. Obviously, this does not occur on well managed obstetric services.

We also inquire whether *prolapse of the cord* occurred, since, when this happens, fetal hypoxia often ensues.

The length of time between *rupture of the bag of waters* and delivery of the baby is used as an index as to whether the labor was long and dry, which increases risk of brain damage, as well as congenital pneumonia with hazard of sepsis and subsequent damage to the brain.

Maternal sedation is an item of interest. Whereas judicious sedation may minimize brain damage by retarding tumultuous labor, oversedation of the mother may result in a narcotized newborn whose respiratory efforts are so diminished that hypoxia occurs on the basis of decreased respiratory effort and inability to clear air passages. Here, again, the degree of sedation is difficult to evaluate in history-taking or in consulting the mother's obstetric record. We always ask, "How long after your baby was delivered did you recover from the effects of the drugs given to you in labor?" Occasionally one obtains information that gives clear evidence that the mother was too heavily sedated.

The type of *anesthesia* is also studied, but the skill of its application is a nebulous consideration. Most women giving information concern-

ing their labor and delivery do not know what anesthetic agents were used.

Maternal shock, or definite hypotension, may result in fetal hypoxia. One thinks of precipitous hypotension sometimes associated with caudal analgesia, shock from bleeding, hypotension from concomitant cardiac failure, and the like.

Many mothers or fathers know *whether the baby required resuscitation* at time of delivery and whether he seemed normal. Physicians delivering babies usually report these facts to the parents and family. Interpretation, however, of the significance of the need for resuscitation, or of mild abnormalities, is difficult. Many babies who require resuscitation subsequently develop normally. Nevertheless, babies who are quite difficult to resuscitate do have a greater chance of hypoxic neurologic damage. Consideration of the maternal obstetric record and the newborn baby's chart is necessary in order to obtain accurate information.

Neonatal Factors

Information about the newborn period is best obtained from the hospital record, but sometimes the informant giving the history of the epileptic child remembers significant portions of the newborn history. This is true because physicians generally orient parents of a newborn baby who has suffered obvious *brain damage*. In taking this part of the history one asks whether the physician stated that there was probably some damage to the baby's brain, whether twitchings or frank seizures occurred, whether the infant seemed unduly limp or rigid, whether spinal puncture was performed, and whether prolonged administration of oxygen was required. Since brain-damaged newborn babies often fail to nurse well, one inquires about interest in nursing and vigor of sucking.

Since kernicterus may produce subsequent convulsive seizures, questions are asked about *severe jaundice* in the first days of life, Rh or ABO iso-immunization, and whether the baby was prematurely born.

Serious illnesses in the newborn infant are often associated with severe dehydration, septicemia or disturbances of electrolyte values, all of which, singly or in combination, may cause brain damage. Therefore one inquires about such events. Some indication of whether the newborn infant was normal is obtained by the question, "How long did your baby remain in the hospital after he was born?" Ordinarily a baby who is permitted to go home from the hospital with his mother is not thought to have incurred obvious damage.

The *presence of gross anomalies* noted in the newborn period suggests that malformation of the child's brain might have occurred also, owing to the fact that adverse prenatal influences producing anomalies often distort growth and development of more than one organ or part of the body.

Postnatal Brain Damage

From the child's medical record, as obtained from hospital records and those of physicians, complemented by the memory of the informant, one inquires about *hydrocephalus* or *other cranial abnormality, meningitis or other central nervous system infection, head trauma* that seemed to be more than trivial, *subdural hematoma* and symptoms currently suggestive of *brain tumor*. Also, questions are asked about possibility of *poisoning*, especially lead poisoning, illnesses that may have been *cerebral vascular accidents*, or *episodes of cerebral hypoxia*, such as may have occurred from *near-drowning, smothering*, illnesses requiring *oxygen therapy*, or periods of *severe dehydration*. Information that the child had an illness requiring intravenous fluid therapy may well point toward the real cause of the brain damage, since severe dehydration may foster subdural collections of fluid,[23] cerebral hypoxia, thromboses or hypernatremic brain damage.[7]

General Pediatric History

Having concluded the first section of the history, pointed specifically toward elucidating the etiology of the convulsive seizures and including questions on family history, prenatal factors, perinatal events and postnatal occurrences, we now obtain a general pediatric history along traditional lines. Information about *serious illnesses* that may have had a bearing on brain damage might have been obtained in the previous section. In questioning about *immunizations* it is important to note severe febrile reactions that may have occurred; the pertussis component of vaccines may cause such reactions that may lead to permanent brain damage.[5] In inquiring about *common contagious diseases* it should be borne in mind that some of them, especially measles and mumps, are at times accompanied by encephalitis that may produce permanent brain damage. *Diet* may have a bearing on seizures, as in neonatal tetany when a relatively high phosphate intake in artificial feedings may have occurred, or in rickets accompanied by hypocalcemic tetany from lack of vitamin D in the diet.

Developmental Progress

Next, the developmental progress of the child is ascertained along the usual lines of motor, language, personal-social and adaptive behavior.[8] Severely brain-damaged children often grow and develop at an abnormally slow rate, although general growth and development proceeds quite normally in many epileptic children who have lesser degrees of brain damage. If the epileptic child is within the usual age range in

which developmental testing is ordinarily done, such examination constitutes a part of the general evaluation of the child. In young children, especially infants, it is often more helpful in eliciting evidence of probable brain damage than is formal neurologic testing.

Mental Status

In each case some idea of the mental status is obtained. For infants and very young children this may best be determined by Gesell-type testing. In children of school age gross information may be derived from their progress in school and from whether they are considered dull or bright. In this connection it is well to remember that lay opinions regarding mental ability of children are often wrong, and that Charles Darwin and Sir Winston Churchill were considered rather ordinary scholars. Also, failure to do well at school may be due to impaired hearing, poor vision, specific reading disability[1] or emotional maladjustment, rather than to an inherently dull mind. The experienced physician will generally know when it is advisable to obtain formal determination of the level of intelligence by special testing. The patient's intelligence has much to do with the degree of his cooperation in management and the ease with which emotional maladjustment may occur or be corrected. Also, when marked mental retardation exists, this may modify to some extent the effort to gain full control of seizures when these seem to defy medical management.

Psychologic Factors

Mention was made previously of the importance of evaluating the psychologic status of the epileptic child. In this respect, epileptic patients are divided into two groups: (1) those in whom emotional maladjustment occurs as a result of the seizures, or from coexisting environmental situations; (2) those in whom the brain damage itself has produced defective emotional control.

Prevention or correction of emotional maladjustment is a fundamental aspect of management of the epileptic child.[3] As soon as the physician is certain that the child has epilepsy he should counsel with the parents in such a way as to minimize harmful attitudes toward the child and his disease. The aims are to eliminate superstitions and erroneous beliefs concerning epilepsy, to explain fully to the parents the nature of the condition and its management, to help them face the problem frankly and confidently, and to warn against overprotection, despondent attitudes and other factors that may lead to emotional distortion.

When analysis of the case indicates that emotional disturbances

already exist, every effort is directed toward their elimination by the usual methods applied in the solution of problems in this sphere. The properly oriented pediatrician or family physician can often do this as well as a consulting psychiatrist, who may not yet have the full confidence of the parents and child and may not be as fully informed of the general aspects of the case. However, there is no doubt that the services of a trained psychologist or psychiatrist are most helpful in severely maladjusted epileptic children, just as they are for badly disturbed children without epilepsy.

Although we do not give every patient a complete psychologic evaluation, we do screen for emotional maladjustment and study more fully those patients in whom there is evidence of such a disturbance. Therefore our routine history includes questions about such items as happiness, unhappiness, tensions, worries, fears, shyness, hostility, aggressiveness, obedience, cooperation and other factors that have a bearing on the child's psychologic adjustment in the home, the neighborhood, the school and the community. Specific behavior problems are noted and studied as part of the over-all evaluation.

The syndrome of the emotionally disturbed child whose behavior is abnormal because of brain damage should receive special attention in the study of the epileptic child. The behavior of such children is characterized by all, or combinations of, the following: short attention span, excessive motor activity, major mood swings, irrascibility, hyperirritability, destructiveness and, in school years, often by specific difficulty in mathematics, a subject requiring sustained attention span.[2] There is a double reason to detect children with this syndrome: (1) to relieve parental guilt sensations arising from their inability to cope with the child's behavior; (2) the hope that certain drugs such as Benadryl, Dexedrine or Benzedrine, or the newer tranquilizing drugs may be of benefit. It has been our experience that the majority of these children have a clearly abnormal electroencephalogram, usually showing generalized cerebral dysrhythmia, whereas children with the ordinary type of behavior problems not based on brain damage usually have normal electroencephalograms.

General Physical Examination

A complete physical examination is made, including data on height and weight, blood pressure determination, and evaluation of the various parts of the body. Such an examination may reveal evidence of associated weakening conditions that may, perhaps through their influence on general body vigor or circulatory efficiency, have some bearing as trigger mechanisms for recurrent seizures. The difficulty lies in evaluating the significance of minor abnormalities encountered. The

general approach is to seek to correct any defects that prevent achievement of robust health.

Neurologic Examination

In the epileptic child this part of the examination obviously has peculiar significance, especially in detection of neurologic evidence of a localized lesion that might possibly be susceptible to subsequent surgical excision. Not all the items of a complete neurologic examination need be listed here, but one notes the general appearance of the child, his behavior, his gait, the shape of his skull and its circumference, and use of special senses, and evaluates the integrity of his cranial nerves, normal and pathological reflexes, motor functions, sensation, and presence or absence of asymmetries, weaknesses, paralyses, spasticity, flaccidity, and the like. Inspection of the eyegrounds is part of this examination.

Description of Convulsions

This part of the history is particularly important from the standpoint of classification of the type, or types, of seizures and for eliciting information as to whether there is probably a localized epileptogenic focus. Also, the severity of the disease can often be ascertained from information gained in this part of the work-up.

One wishes to know the *date of the first convulsion and the age of the patient at that time,* since age at onset has some bearing on probable etiology of the seizures.[20, 21] For example, convulsions dating from the newborn period, or even the first two years of life, are most often due to birth trauma and sequelae, febrile convulsions rarely occur after three years of age, and essential or cryptogenic epilepsy becomes more common as the years advance.

Determination of the average *frequency of seizures* gives important information about severity of the epilepsy and is helpful in knowing approximately how long it may take to determine efficacy of drug therapy. For instance, if a patient has an average of one grand mal seizure a week, it will usually not take long to find out what drugs in what doses are needed for this particular patient. If seizures occur on an average of once each six months, however, one may treat for half a year before knowing whether the drug, or drugs, selected will help subdue the seizures. Determining frequency of seizures before treatment is started also gives a base line against which to evaluate subsequently the degree of seizure control.

One should inquire about the time of day or night when seizures have the greatest tendency to occur. This information is especially im-

portant in guiding opinion as to whether hypoglycemia is likely to be the causative factor, as may be true when seizures usually occur hours after eating.

In some instances *precipitating factors* trigger the epileptic attack. Successful management of the case may depend upon determining and eliminating these factors. One may mention such things as *fever, infections, emotional upsets, bright* or *flickering light* (photic epilepsy), *hyperventilation, premenstrual tension,* undue *fatigue,* gross *overeating,* excessive *fluid intake,* and relation of seizures to *sleep.*

Although many children cannot recall an *aura* before the attack, inquiry is made about this and its nature determined. Such information may help localize an epileptogenic focus.

An exact description of the patient's seizures is now obtained. Possibly he may have more than one type of seizure, as in the familiar example of mixed grand mal and petit mal epilepsy. Sometimes the informant's description of the attack is too indefinite to permit decision as to type of seizure, and one may have to await observation of an attack, or further details from the informant. Intelligent parents, however, can generally give diagnostically useful information about the seizures.

Sometimes, however, the parents cannot tell whether the child has actually had seizures. This is especially true when the convulsions occur only at night. One may gain information here by inquiring whether the child cries out in his sleep, whether he awakens with a painful tongue (from biting it during a seizure), whether blood or saliva is found on his pillow, and whether he awakens with a bad headache.

Postictal manifestations should receive attention. Localized weakness or paralysis after an attack (Todd's paralysis) may point to a localized epileptogenic focus. Headache, stupor and sleepiness suggest that a grand mal seizure occurred. Abnormal behavior with amnesia for the event is characteristic of psychomotor epilepsy.

Classification of Seizures

Although there is no general agreement on classification of convulsive seizures, we use the classification given below. Opposite the type, or types, of seizures applicable to the patient under consideration we write, "Clearly this type," or "Probably this type," or "Possibly this type," depending upon how certain we are of the proper classification. Such opinions are revised when further experience with the patient merits it.

CLASSIFICATION OF SEIZURES

I. Grand mal (generalized)
   May have tonic-clonic, tonic, clonic, atonic types (includes status epilepticus)
   A. Organic
   B. Idiopathic

II. Petit mal (to be true idiopathic, must be associated with 3-per-second spike and dome EEG record)
  A. Lapse
    1. Organic
    2. Idiopathic
  B. Myoclonic
    1. Organic
    2. Idiopathic
  C. Akinetic
    1. Organic
    2. Idiopathic
III. Massive spasms (infantile spasms, jack-knife attacks, infantile myoclonic seizures)
IV. Focal motor (includes jacksonian)
V. Psychomotor (temporal lobe seizures)
VI. Equivalents (diencephalic, thalamic, hypothalamic)
VII. Mixed (more than one of the above clinical types in same patient)
VIII. Miscellaneous types (not chronic) (should not be called epilepsy)
  A. "Febrile convulsions"
  B. Miscellaneous, such as hypoglycemia, renal disease, hypocalcemia

Laboratory Findings

The extent to which laboratory data are needed depends upon the individual case and the discretion of the physician. A routine urinalysis and complete blood cell count are obtained on all patients. Skull roentgenograms and electroencephalograms are also obtained. The skull films are usually normal, but occasionally one detects unsuspected evidence of increased intracranial pressure, intracranial calcifications or asymmetry of the skull that was not noted on physical examination. The electroencephalogram is not used in order to determine the type of the patient's seizures, although it may reveal characteristic evidence of petit mal epilepsy, but more to look for further localizing evidence of an epileptogenic focus, and to give information concerning the degree of diffuseness of the cerebral abnormality. There is much dispute about correlation of the electroencephalogram and the clinical seizure. A carefully taken history, perhaps aided by observation of an attack, generally suffices to determine type of seizure.

Further laboratory tests may be requested, depending upon the nature of the case and the probability of an underlying mechanism causing the seizures. For example, one may request determination of blood nonprotein nitrogen as a screening test for renal insufficiency. If it is elevated, determinations of levels of calcium and phosphorus are indicated, since renal insufficiency is often accompanied by hypocalcemia and hyperphosphatemia, and hypocalcemia may cause seizures.

When the history suggests the possibility of hypoglycemia as the cause of the seizures, studies of factors regulating the blood glucose level should be made. One must remember, however, that laboratory investigation of possible hypoglycemia is time-consuming and expensive,

and that only a small percentage of epileptic patients have seizures on this basis. The chief error that leads to too many investigations for hypoglycemia is the erroneous impression that most seizures occurring during the early morning hours before breakfast are related to hypoglycemia. In reality, most of these dawn attacks seem related to the cerebral instability present when the patient is coming from deep sleep to lighter sleep before awakening. One must realize that approximately 20 per cent of epileptic patients have nocturnal seizures and that only a small number of these patients have hypoglycemia. Often one can eliminate hypoglycemia from consideration by obtaining a history showing no relationship of seizures to fasting, as when the patient is known to have had some of his attacks toward the end of meals or immediately thereafter. These remarks are not made to decry consideration of hypoglycemia, but merely to urge clinical common sense.

A serologic test for syphilis should be obtained, although syphilis is now truly the "vanishing American." Since routine tuberculin testing is advisable for all children anyway (unless the child is known to have had a previous positive reaction), such a test may be performed, but will rarely be of any value in diagnosis. Tuberculoma of the brain has now become a great clinical rarity.

Anemic, epileptic Negro children should have a test for sickling of erythrocytes, since sickle cell disease often produces brain damage.[10, 12]

If chorioretinitis is present, or hydrocephalus, or cerebral calcifications in skull roentgenograms, or any combination of these findings, the Sabin-Feldman dye test for toxoplasmosis should be done.

Depending upon the merits of the case and clinical judgment in appropriate situations, some patients require cerebral angiography or pneumoencephalography. It would defeat the purpose of this presentation to summarize indications for each of these procedures, or to elaborate further on what tests might be needed in a particular patient with epilepsy.

Condensed Analysis of the Case

After the work-up described in the previous pages has been completed, one is now ready to summarize the key positive findings so that brief study of this section of the record will give the important elements of the case.

Treatment Prescribed

In this section one lists the drug, or drugs, to be used, their dosages and timing of doses, and briefly describes what advice was given in regard to diet, hygiene and psychologic factors.

Further Studies That Might Be Indicated

After the initial work-up of the patient has been completed one notes in this section what further studies might deserve future consideration.

Progress Notes at Subsequent Visits

Our record form ends with a series of six half-page spaces for progress notes at subsequent visits. Such notes include information on changes in the patient's condition, frequency of seizures, change in type of seizure, regularity of medication, toxic reactions to drugs, weight of patient, and any other information considered pertinent. The treatment the patient is now to be given is described in the note.

SUMMARY AND CONCLUSIONS

1. The importance of a comprehensive evaluation of the epileptic child has been presented through consideration of a special Children's Convulsive Seizure Record Form used in the Children's Convulsive Seizure Clinic of the University of Tennessee. It constitutes an integral part of the combined hospital and outpatient department records.

2. This form features an orderly analysis of the case from the standpoints of family history, prenatal factors, perinatal factors, postnatal events, general pediatric history, developmental progress, mental status, psychologic aspects, general physical examination, neurologic examination, information concerning details of the patient's seizures, classification of the seizures, laboratory investigation, condensed analysis of the case, treatment prescribed, further studies that might be indicated, and subsequent progress notes.

3. Far from being unduly complicated, this form facilitates the recording of pertinent information in appropriate sequence, thereby simplifying subsequent analysis of the record.

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THE DRUG THERAPY OF EPILEPSY

With Special Reference to Newer Drugs

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Although many classifications have been proposed, I have found the following general classification of the various types of epilepsy to be of value to clinicians, since some forms of epileptic seizures are more amenable to action of specific drugs than others.

1. *Idiopathic epilepsy*, in which the most frequent type of attack is one of the following:
   (a) Grand mal
   (b) Petit mal (more common in children)
   (c) Psychomotor (more common in adults)
   (d) Other equivalents, e.g., abdominal epilepsy, migraine, trance states, visceral symptoms, etc.
2. *Symptomatic or organic epilepsy*, in which the most frequent type of attack is of the following nature:
   (a) Jacksonian or focal
   (b) Akinetic
   (c) Myoclonic
   (d) Any of the forms seen in idiopathic epilepsy

PRINCIPLES OF DRUG THERAPY

It is important to keep in mind that the therapy of epilepsy requires more than drug therapy alone. Control of other factors is necessary, such as the numerous trigger mechanisms which exist in a person who has a convulsive diathesis; for example, emotional tensions and disturbances; frustrations; fever, gastrointestinal upsets; excessive intake

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of fluids, especially alcohol; constipation; and allergic episodes. Occasionally the number of seizures will increase during some phase of the menstrual cycle. Simple boredom, nurtured by the deadly lack of occupation or recreation, may increase the tendency to seizures. Frequently the practice of general hygienic measures and psychiatric care are more important than drug therapy in controlling seizures. In general, seizures associated with other evidence of organic brain disease are more refractory to drug therapy than are the "idiopathic" type of seizures. The adoption of surgical procedures, such as the extirpation of discharging cortical foci, should be considered only when medical management has failed and spells are of a focal nature.

Modern drug therapy of epilepsy began 100 years ago, when bromides were first used by Locock in 1853. Phenobarbital was introduced by Hauptman in 1912, and Dilantin Sodium by Merritt and Putnam in 1937. Ever since Tridione and Mesantoin were investigated in 1944, a series of additional drugs, such as Paradione, Phenurone, Mebaral, Gemonil, Prenderol, Celontin, Mysoline, Milontin, Miltown, Diamox and Peganone, have been introduced. Chemically, many of these drugs are derivatives of urea. By virtue of an interchange of methyl, ethyl and phenyl radicals, both the specific effectiveness and the toxicity of these drugs have been modified. For convenience, the clinical efficacy of the various drugs according to type of seizure is summarized in Table 21.

It is advisable to begin with a single drug in epilepsy, gradually increasing the dose until either control or maximum effect is achieved, or a dose is reached beyond which toxic symptoms develop. If this medication results in partial improvement, the relative improvement is maintained by continuing the drug while adding another to the therapeutic regimen. Some patients respond better to one drug, some to another, and still others to a combination of drugs. In the event that a drug is to be discontinued, it should be withdrawn slowly so as to prevent precipitation of a status epilepticus. Some drugs effective in controlling one type of seizure may aggravate or precipitate another type. Finally, it is axiomatic that the antiepileptic effect produced by medication should precede the toxic effect, and that any drug that produces a toxic effect (and this includes drowsiness) before it establishes a therapeutic effect is not ideal.

Anticonvulsant medication is usually prescribed three times a day. Occasionally this is reduced to two doses, while in instances in which drugs are rapidly eliminated, four to five daily doses are prescribed. When all spells occur nocturnally, it is permissible to prescribe a single dose before the patient retires. For special occasions inducing stress or excitement—birthdays, holidays and menstrual periods—it may be necessary to increase dosages temporarily.

The prime objective of drug therapy is to achieve a clinical cure rather than an electroencephalographic cure. Except for Tridione and possibly some of the newer drugs, none of the drugs extant affect the electroencephalographic findings as markedly as they do the clinical picture; in other words, even in the presence of a continuing electroencephalographic dysrhythmia, it is possible to have a completely favorable clinical remission.

Because of the toxic potentialities of many of the new effective anticonvulsant drugs, close medical supervision is required in their use. It is important that physicians read carefully the literature supplied by manufacturers of these drugs regarding possible toxic effects and guide themselves accordingly. Unfortunately, not all pharmaceutical manufacturers stress the dangerous aspects sufficiently.

EFFICACY OF INDIVIDUAL DRUGS

As indicated above, some drugs have greater specificity for certain types of seizures than others. In the treatment of grand mal, the initial drugs of choice are *phenobarbital* (phenyl-ethyl-barbituric acid) and *Dilantin Sodium* (sodium diphenylhydantoinate), both of which have a greater anticonvulsant effect than do other barbiturates or the bromides. Although manifesting a strong anticonvulsant effect, Dilantin frequently increases and even precipitates petit mal attacks, a form of seizure found much more frequently in children than in adults. On the other hand, phenobarbital has no tendency to increase petit mal attacks, but does occasionally aggravate psychomotor attacks, a form of seizure rare in children and more characteristic of adults. Hence in children afflicted by grand mal seizures, phenobarbital is the initial drug of choice, while in adults with grand mal, Dilantin is preferable. By the same token, a patient having a combination of grand and petit mal seizures would be expected to respond more favorably to phenobarbital; whereas in coexistence of grand mal and psychomotor seizures, Dilantin is the drug of choice.

Of the common sedating barbiturates, phenobarbital exerts an antiepileptic effect out of all proportion to its soporific action. Children tolerate relatively larger dosages of this drug per pound of body weight than do adults. When seizures are controlled by phenobarbital, no other medication is necessary; however, if control of epilepsy is only partially achieved, Dilantin or some other suitable drug may be added. Should phenobarbital not exert a beneficial effect, substitution of another drug is indicated.

Drowsiness is the most common side effect produced by phenobarbital therapy; it can be combated by Benzedrine or Dexedrine should it be desirable to continue the use of phenobarbital. Rashes may occur,

TABLE 21. *Clinical Efficacy of Drugs According to Type of Seizure*

DRUG	CHEMICAL FORMULA	AVAILABLE FORM	DOSAGE		THERAPEUTIC EFFECTS				ILL EFFECTS
			Amount	Times Daily	Grand Mal	Petit Mal	Psychomotor	Myoclonus	
Phenobarbital	Phenyl-ethyl-barbituric acid	Tablets, 0.015, 0.03, 0.06 and 0.1 gm. Elixir, 0.015 gm. /tsp.	0.015–0.1 gm. (¼–1½ gr.)	2–4	++++		A* (occas.)	±	Drowsiness
Dilantin (Parke, Davis)	Sodium 5, 5-diphenyl hydantoinate	Capsules, 0.03, 0.1 gm. Capsules in oil, 0.1 gm. Delayed action capsules, 0.1 gm. Infantabs, 0.05 gm. Suspension, 0.1 gm./tsp.	0.03–0.1 gm. (½–1½ gr.)	2–4	++++	A	+++	±	Ataxia, diplopia, gingivitis, rash
Mesantoin (Sandoz)	3-methyl-5, 5-phenyl-ethylhydantoin	Tablets, 0.1 gm.	0.05–0.1 gm. (¾–1½ gr.)	2–4	+++	+	+	±	Rash, drowsiness, blood changes, hepatitis
Bromide	Sodium, potassium and ammonium bromide	Tablets, 0.3, 0.6, 1 gm. Elixir, 1 gm./tsp.	0.3–1 gm. (5–15 gr.)	2–4	++	+			Rash, confusion
Mebaral (Winthrop Stearns)	N-methyl-ethylphenyl-barbituric acid	Tablets, 0.03, 0.1, 0.2 gm.	0.03–0.2 gm. (½–3 gr.)	2–4	+	+			Drowsiness
Phenurone (Abbott)	Phenacetyl-carbamide	Tablets, 0.3, 0.5 gm.	0.25–1 gm. (4–15 gr.)	2–5	++	++	++++		Hyperexcitability, personality disturbances, rash, fever
Tridione (Abbott)	3,5,5-trimethyl oxazolidine-2,4-dione	Capsules, 0.3 gm. Dulcet, 0.15 gm. Elixir, 0.15 gm./tsp.	0.15–0.6 gm. (2½–10 gr.)	2–4	A	++++	+		Visual disturbances, rash, blood changes, toxic Mesantoin synergy

Paradione (Abbott)	3,5-dimethyl-5-ethyl oxazolidine-2,4-dione	Capsules, 0.3 gm. Liq. Conc., 0.3 per cc.	0.15–0.3 gm. (2½–5 gr.)	2–4	A	++	+		Blood changes, rash, toxic Mesantoin synergy
Prenderol† (Squibb)	2,2-diethyl-1,3-propanediol	Tablets, 0.5 gm.	0.5–1 gm. (7½–15 gr.)	4–5	A	+++			None to date
Gemonil (Abbott)	5,5-diethyl-1-methyl-barbituric acid	Tablets, 0.1 gm.	0.05–0.2 gm. (¾–3 gr.)	2–4	+	±		++++	Drowsiness
Mysoline (Ayerst)	5-phenyl-5-ethyl-hexahydropyrimidine-4:6 dione	Tablets, 0.25 gm. Suspensions, 0.25 gm./tsp.	0.125–0.5 gm. (2–7½ gr.)	3–4		++++	++		Somnolence, ataxia
Milontin (Parke, Davis)	N-methyl-α-phenyl-succininimide	Tablets, 0.3 gm. Suspensions, 0.25 gm./tsp.	0.3–0.6 gm. (5–10 gr.)	2–4		++			Nausea, ataxia, dizziness, hematuria
Celontin (Parke, Davis)	Methsuximide	Capsules, 0.3 gm.	0.3 gm. (5 gr.)	2–4		++	+++		Ataxia, drowsiness
Diamox (Lederle)	2-acetylamino-1,3,4-thiadiazole-5-sulfonamid	Tablets, 0.25 gm.	0.125–0.250 gm.	2	+	++			Drowsiness, rash, blood changes
Miltown (Wallace)	2-methyl-2-3-propyl-1,3-propanediol dicarbamate	Tablets, 0.2, 0.4 gm.	0.1–0.8 gm. (1½–12 gr.)	2–4	A	++++			Drowsiness
Peganone (Abbott)	3-ethyl-5-phenylhydantoin	Tablets, 250 mg.	125–250 mg. (2–4 gr.)	2–4	++			+	Occasional rash, some gastrointestinal disturbances
Ketogenic diet			F.A./G-2.7 to 3.1			++++			Difficult to administer at home

* A = Aggravates.
† = Must be given with a retarder.

although they are rare in children and more common in adults. In children who manifest behavior disturbances characterized by hyperactivity, phenobarbital may display a paradoxical effect, aggravating the hyperexcitability. The distinct advantage demonstrated by phenobarbital lies in its relative nontoxicity and in its low cost. Phenobarbital is available in a profusion of sizes and forms, including elixirs, candy combinations, delayed action capsules as well as tablets of ¼, ½, 1 and 1½ grain sizes.

Dilantin Sodium (sodium diphenyl hydantoinate) is commercially available in 0.03 gm. (½ grain) and 0.1 gm. (1½ grain) capsules, in 0.05 gm. (¾ grain) candy form, and in liquid emulsion form containing 0.1 gm. (1½ grains) to the teaspoonful. It is also available in the delayed action form as 0.1 gm. (1½ grains) of enteric capsules. Its toxic effects include vertigo, dizziness, diplopia, ataxia, hyperplasia of the gums, skin rashes and occasionally hirsutism. As Dilantin Sodium is strongly alkaline, it sometimes causes gastrointestinal upsets. These may be alleviated by small amounts of orange juice or by mixing the drug with food. Dilantin in oil, 0.1 gm. (1½ grains), causes fewer gastrointestinal upsets and, because of the "retarding" action of the oil, tends to be effective over longer periods than does unalloyed Dilantin. For patients subject only to nocturnal seizures, when an even longer period of effective action is desired, Dilantin, delayed action, 0.1 gm. (1½ grains), may be given at bedtime.

Mesantoin (methyl-phenyl-ethyl hydantoin), one of the newer drugs related to Dilantin, is frequently more effective, especially in epilepsy due to organic brain disease. Although Mesantoin causes much less gingivitis, diplopia and ataxia than does Dilantin, it is more likely to cause rashes, including exfoliative dermatitis, agranulocytosis and occasionally hepatitis. It is fairly safe for use in children, however. Unlike Dilantin, Mesantoin does not tend to precipitate petit mal spells; in some instances it actually controls them. Moreover, Mesantoin is often more effective than either Dilantin or phenobarbital in patients having a combination of grand mal and petit mal. Attention should be called to a danger in the use of Mesantoin which has not been publicized. This is its synergistic toxic action when administered together with Tridione or Paradione. Consequently, Mesantoin should never be prescribed in combination with Tridione or Paradione, since the toxicity of the two groups of drugs is enhanced when they are taken together. Mesantoin is obtainable in scored 0.1 gm. (1½ grains) tablets. Some patients respond best to phenobarbital, some to Dilantin, others to Mesantoin, and still others to a combination of two or even three of these drugs. Since Mesantoin and phenobarbital both cause drowsiness, this side effect is enhanced when they are taken together.

Mysoline (5-phenyl-5-ethyl-hexahydropyrimidine-4:6-dione) is of defi-

nite value in the treatment of many forms of grand mal uncontrolled by other drugs; it is supplied in 0.25 gm. scored tablets and as an emulsion containing 0.25 gm. per dram. It is prescribed in dosages of 125 to 500 mg. (½ to 2 tablets) taken three or four times daily. A drawback to its use is the tendency to cause somnolence and ataxia. Thus it is well to start with small dosages, gradually increasing the amount to the point of tolerance. It has relatively few serious toxic effects.

Peganone (3-ethyl-5-phenyl hydantoin), recently made available, is mainly useful in grand mal and somewhat effective in psychomotor seizures. There are no side effects except for occasional rash, some gastrointestinal disturbances, such as a burning sensation and lightheadedness; there is no adverse effect on the hemapoietic system. The drug can be used in combination with most of the other anticonvulsants, although it has been noted that when used with Phenurone, an exacerbation of paranoid tendencies has been evinced. Although Peganone is not as effective as Dilantin, phenobarbital or Mysoline in controlling grand mal, it has been found valuable, particularly as an adjuvant drug. It does not cause normalization of the electroencephalogram, and is of no benefit in petit mal. It is available in scored tablets of 0.25 and 0.50 gm. (3¾ and 7½ grains).

There are several other hydantoin analogues that possess some anticonvulsant effect, but none of them to a degree as extensive as those already described.

Bromides are less effective than any of the previously mentioned drugs in the control of grand mal seizures; occasionally, however, they inhibit seizures unaffected by the use of other drugs. Bromides in the form of sodium salts, or as a mixture of equal parts of sodium, potassium and ammonium bromides, are prescribed in dosages of 0.33 to 1 gm. (5 to 15 grains) taken three times daily, or until such time as a blood bromide level not more than 100 mg. per 100 ml. is reached; higher levels may prove toxic. The side effects produced by bromides include drowsiness and confusion. Acneiform bromoderm, a troublesome symptom, is seen frequently, especially in adolescent girls. Should a bromide rash appear, the drug is discontinued and the sodium chloride intake is increased.

Mebaral (N-methyl-ethyl-phenyl-barbituric acid) has some anticonvulsant action and may occasionally control petit mal seizures and the focal seizures of hemiplegics. It produces less sedation than phenobarbital, and can generally be prescribed in dosages twice the amount of phenobarbital. Other than drowsiness, no ill effects have been observed following its use. Mebaral is available in 0.03, 0.1 and 0.2 gm. (½, 1½ and 3 grain) scored tablets.

Tridione (3, 5, 5-trimethyl oxazolidine-2, 4-dione) is the most effective drug yet introduced in the treatment of petit mal seizures. Since petit mal seizures have always been less amenable to drug therapy than

grand mal, this drug met a pressing need. The effect of Tridione on petit mal is frequently spectacular. Normalization of the electroencephalogram occurs more frequently with Tridione therapy than with any other drug. In addition, it is also affective in several conditions associated with basal nuclear lesions; for example, in some cases of athetosis and in certain behavior disturbances. Its favorable therapeutic action in petit mal lends a modicum of credence to the hypothesis that petit mal seizures originate not in the cortex, but in the midbrain. Tridione is available as 0.3 gm. (5 grain) capsules, as an elixir containing 0.15 gm. (2½ grains) to the teaspoon, and in dulcet form, containing 0.15 gm. to the dose. Approximately 70 per cent of the patients with idiopathic petit mal are benefited by the preparation; in children manifesting petit mal associated with organic brain disease, the percentage of success is considerably less.

Unlike Dilantin or phenobarbital, Tridione does not produce exacerbation of symptoms on withdrawals, although it occasionally precipitates or aggravates grand mal seizures. Hence in patients in whom petit mal and grand mal coexist, Tridione should not be prescribed alone, but rather in combination with either phenobarbital or Dilantin. As already pointed out, its use in combination with Mesantoin is dangerous because of a synergistic increase in toxicity. The most common toxic symptoms attributable to Tridione are blurring of vision, and bright-light blindness or hemeralopia. In some instances morbilliform and exfoliative rashes occur. More serious complications involve blood and bone marrow, with leukopenia and agranulocytosis as side effects; fatalities have also been reported in the medical literature. Side effects occur in 30 to 40 per cent of adults, but fortunately in only 10 per cent of children, among whom petit mal has a higher incidence. Patients taking Tridione should have blood cell counts at least once a month. A white blood cell count less than 3000 is an indication for stopping the drug.

When control is incompletely established, the remaining seizures are often of longer duration and greater severity than those originally extant. This would indicate that more than one kind of petit mal seizure exists.

Paradione (3, 5-dimethyl-5-ethyl-oxazolidine-2, 4-dione), an analogue of Tridione, is somewhat less effective than Tridione in the treatment of seizures, but may sometimes control petit mal when Tridione is ineffective. Paradione appears to be more effective than Tridione in controlling petit mal due to organic brain disease. Fewer side effects are produced by Paradione than by Tridione, with less disturbance of vision and fewer rashes. Toxic effects on the blood occur occasionally. Paradione is available in 0.3 gm. (5 grain) soft elastic capsules, and as a liquid concentrate containing 0.3 gm. per cubic centimeter. The drug is most effective when prescribed in combination with Prenderol. It

may also be given with phenobarbital or Dilantin. As previously noted, it should not be combined with Mesantoin, since a synergistic toxic effect may be produced. As with Tridione, patients receiving Paradione should have periodic blood cell counts.

Prenderol (2, 2-diethyl-1, 3-propanediol) is a valuable adjuvant in the treatment of petit mal seizures. Although it is less effective than Tridione, it is more effective than Paradione and often controls idiopathic petit mal seizures which Tridione and Paradione have been unable to stop. Because of its rapid absorption and rapid excretion, Prenderol must be given with a "retarding" agent. We have found one tablespoonful of 32 per cent (whipping) cream (or its equivalent in other fats or oils) given with each dose of Prenderol to be an effective retarder. Among noncaloric retarders, PVP (polyvinylpyrrolidone) powder or carbomethyl cellulose in one tablespoonful dosages has been found to be most effective. These will delay Prenderol absorption and consequently prolong its antiepileptic effect for three to five hours. Prenderol is available in a 0.5 gm. (7½ grain) scored tablet. The usual dose is 1 gm. taken four times daily along with a dose of one of the aforementioned "retarders." Prenderol has a synergistic action with both Paradione and Tridione, especially the former. A combination of Prenderol with either of the "diones" may control petit mal seizures uninfluenced by either drug alone. The value of Prenderol appears to lie in its relative lack of toxicity. Were it not for the inconvenience caused by the need to use a retarding agent, it would be the drug of choice in petit mal, for, though less effective than Tridione, it is relatively nontoxic. Very large doses cause nausea or dizziness. Like the "diones," Prenderol may precipitate grand mal seizures when it controls the petit mal attacks.

Milontin (methyl-phenyl-succinimide) has some clinical value in controlling petit mal seizures. Less effective than any of the above mentioned drugs in the control of the idiopathic form of petit mal, it is more effective in petit mal due to organic brain disease. However, it is often causes ataxia, dizziness and nausea in a large proportion of cases. A nephrotoxic effect has also been described. Milontin is supplied in 0.5 gm. (7½ grain) capsules and in suspension form containing 250 mg. to the teaspoon. It is prescribed in dosages of 0.3 to 0.6 gm. (5 to 10 grains) to be taken three to four times daily.

Miltown (meprobamate), a tranquilizing agent, has also been found to be of benefit in the petit mal form of epilepsy. Its effectiveness is not as great as that of Tridione, but it is more effective than Paradione, Milontin, or Prenderol used with retarders. The advantages of the drug are that it is the least toxic of all drugs used for petit mal epilepsy and need not be given with any retarders, since its time of effective action is from three to five hours. The only side effect is a drowsiness when it

is given in dosages beyond tolerance. It is available in tablets of 200 and 400 mg., and is administered in dosages of 100 to 800 mg. two to four times daily. Unlike Prenderol, it has no synergistic action with Paradione or Tridione. Unlike Tridione, it does not tend to normalize the electroencephalogram. It may act in part by reducing emotional tension and thus removing many of the trigger mechanisms which precipitate petit mal spells. Because of its relative nontoxicity, it must at present be considered the drug of first choice in petit mal epilepsy. Because of the intense bitter taste of Miltown, it may sometimes be difficult to administer to children who are unable to swallow pills. It is best disguised in sugar and cinnamon put into apple sauce, ice cream or chocolate syrup. Miltown has a tendency to precipitate or aggravate grand mal. The other tranquilizing drugs such as Thorazine and Serpasil do not have the same antiepileptic affects as does Miltown. Occasionally, however, epileptic patients who are given Thorazine may experience a decrease in the number of spells, due perhaps to the blunting of the emotional triggering mechanism.

Antibiotics occasionally have given beneficial results in the control of seizures associated with organic brain disease. Thus Chloromycetin, Aureomycin and Terramycin, when given over a period of several weeks in dosages of 100 to 250 mg., four times a day, may occasionally be beneficial in improving refractory cases. The antibiotics, however, are not effective in over 5 to 10 per cent of cases.

Diamox (acetazolamide) is a sulfonamide derivative which is occasionally of benefit in petit mal epilepsy. The rationale for its use is that it is a carbonic anhydrase which acts as an acidifying agent, and petit mal seizures are often precipitated by alkalosis as may be caused by hyperventilation. The drug is available in 250 mg. scored tablets. Since the effective time of action is about 12 hours, it need be given only about twice a day at the most, in dosages of 1 to 1½ tablets. Diamox may also occasionally benefit grand mal seizures. No definite pattern has emerged for prognosticating the type of seizure for which this drug may be beneficial. As Diamox is a sulfonamide derivative, it is not surprising that occasional rashes and bone marrow damage have resulted from its use.

Acidifying drugs, such as ammonium chloride and glutamic acid, have been found to display questionable beneficial effect in petit mal. As a rule, acidification is not effective unless it is part of a ketogenic diet. A *ketogenic diet* has considerable value in petit mal and is particularly beneficial to young children, although it is difficult to administer at home.

Among other drugs which have been reported to have some benefit in petit mal are caffeine, the amphetamine derivatives, Atabrine and some of the antihistaminics. Although an occasional case of petit mal

may be benefited by any of these drugs, none of them is truly dependable.

The most effective drug next to Dilantin in the treatment of psychomotor epilepsy is *Phenurone* (phenacetyl-carbamide). Furthermore, Phenurone may be of benefit in either grand mal or petit mal; hence it is an all-purpose drug. Phenurone controls approximately 50 per cent of psychomotor, 40 per cent of grand mal and 30 per cent of petit mal seizures. It is obtainable in 0.5 gm. (7½ grain) scored tablets, and as enteric-coated 0.3 gm. (5 grain) tablets. Its mode of action in the case of psychomotor seizures is unknown. Among the side effects of Phenurone is a peculiar hyperexcitability that borders on the psychotic, resembling the type frequently seen in postencephalitic cases. Rashes, which are not uncommon in children, are morbilliform, usually appearing about a week after medication has begun, and preceded by one or two days of fever. After the drug has been withdrawn, the rash disappears; it can be made to reappear with a single dose of Phenurone.

Celontin (methsuximide) is chemically related to Milontin. This drug is of benefit in both psychomotor and petit mal forms of epilepsy. It does not tend to precipitate grand mal spells, as many of the other anti-petit mal drugs do. Although it is not as effective as either Dilantin or Phenurone in control of psychomotor spells, it is a valuable adjuvant when the above-mentioned drugs are not effective. The drug has about the same order of benefit for petit mal seizures as Milontin. As with Milontin, there may be some ataxia and drowsiness as side effects. In high dosages there may be some confusion and depression. Although blood changes have not been common, the drug is so new that it is wise to do routine blood tests. Celontin is available in a capsule containing 0.3 gm. (5 grains), and is given in dosages of 1 capsule two to three times daily.

Other drugs which may benefit patients with psychomotor epilepsy include Mysoline, Mesantoin and Tridione.

A drug that exhibits interesting properties is called *Gemonil* (diethyl methyl-barbituric acid). This drug evinces the unique property of being more effective in the control of seizures associated with organic brain disease than in idiopathic epilepsy. It greatest therapeutic effect is in cases of infantile myoclonic spasms. In this condition it is more selectively beneficial than any other drug. Gemonil may also be effective in the focal seizures of hemiplegics. The drug is available in 0.1 gm. (1½ grain) scored tablets; and is prescribed in dosages twice that of phenobarbital. The only side effect so far detected has been drowsiness with large doses.

Several other drugs that offer promise of effective antiepileptic action are now under investigation, but experience with them has been too limited to include in this discussion. For purposes of clarification,

Table 21 provides the names, formulas, indications, toxic effects and dosages of the drugs discussed.

A categorical generality regarding drug therapy in epilepsy might be stated as follows: Idiopathic forms of epilepsy are more amenable to drugs than are forms due to organic brain disease. In the presence of organic brain disease, unexpected and contradictory drug actions are encountered. Thus Tridione and Paradione are occasionally more effective than Dilantin or phenobarbital in controlling grand mal seizures; similarly, phenobarbital and bromides may be more effective than Tridione in controlling petit mal seizures. Akinetic and myoclonic seizures are among the most difficult epileptic symptoms of organic brain disease to treat. In these conditions various combinations of drugs should be used before a patient is considered not amenable to drug therapy.

The therapy of epilepsy is an individual problem; one patient's seizures may be controlled by a specific drug which may be ineffective in another patient having similar seizures. All the drugs have some objectionable features, either in the form of side effects or the tendency to aggravate certain types of seizures. Knowledge of the drug to be used, the trial and error method of its administration, patience, and, above all, an understanding and control of all factors involved in the care of each patient, still remain the most favorable method of treatment of the epileptic syndromes.

SUMMARY

1. Phenobarbital is the drug of choice for treatment of grand mal seizures in children, while Dilantin is the drug of choice in adults, as are combinations of the two drugs.

2. Mesantoin and Mysoline are the drugs of choice when grand mal and petit mal co-exist. The former exerts a synergistic toxic effect when administered with Tridione or Paradione.

3. Bromides, Phenurone, Mebaral or Peganone may be used when none of the above-mentioned drugs is effective.

4. Tridione is the most effective drug for the treatment of petit mal. Paradione is less effective and less toxic than Tridione. Both drugs exert a synergistic toxic effect when given with Mesantoin.

5. Next to Tridione, Miltown is the most effective drug in petit mal. Because it is so much less toxic than the dione group, it might be wise to consider it the drug of first choice for petit mal.

6. Prenderol administered with a retarder is effective in controlling petit mal seizures. It has a synergistic beneficial effect with Paradione and Tridione.

7. Milontin, Celontin and Diamox may occasionally be useful in petit mal when other drugs fail.

8. Peganone is useful as an adjuvant drug in grand mal and has few side effects.

9. Phenurone is an all-purpose drug, being most effective in psychomotor spells. Dilantin, Mysoline and Celontin are also useful in controlling psychomotor spells.

10. Gemonil possesses the unique property of being more effective in organic brain disease than in the idiopathic form of epilepsy, and is especially useful in infantile myoclonic spells due to organic brain disease.

11. When single drugs are ineffective, combinations of drugs should be tried.

12. Physicians should be alert to the toxic potentialities of anticonvulsant drugs and aware of the occurrence of side effects. When Tridione, Paradione, Mesantoin or Phenurone is prescribed, periodic blood cell counts are essential. Evidence of leukopenia below 3000 is an indication for discontinuance of medication.

13. Control of hygienic and psychiatric factors is important as an adjunct to the drug therapy of epilepsy.

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